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THE WESTERN Journal of Medicine

VOLUME 133 • NUMBER 1 JULY 1980

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2. Sun DCH: Etiology and pathology of p ulcer, chap. 27, in *Gastroenterology*, ed edited by Bockus HL, *et al.* Philadelph W.B. Saunders Company, 1974, pp. 579

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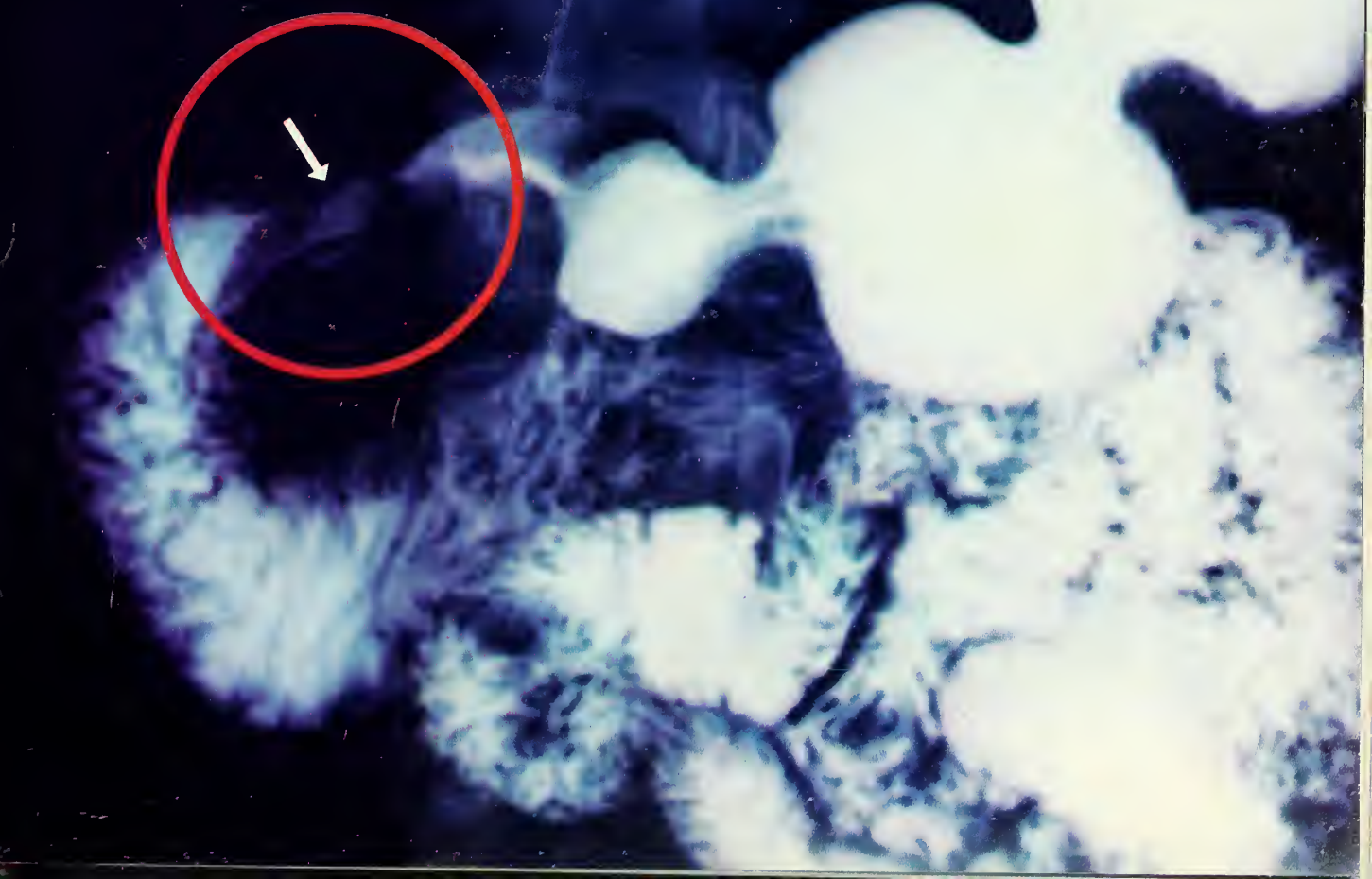

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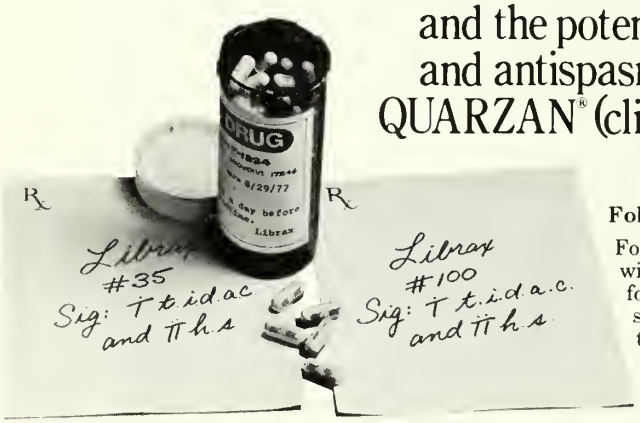

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Final classification of the less-than-effective indications requires further investigation.

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Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

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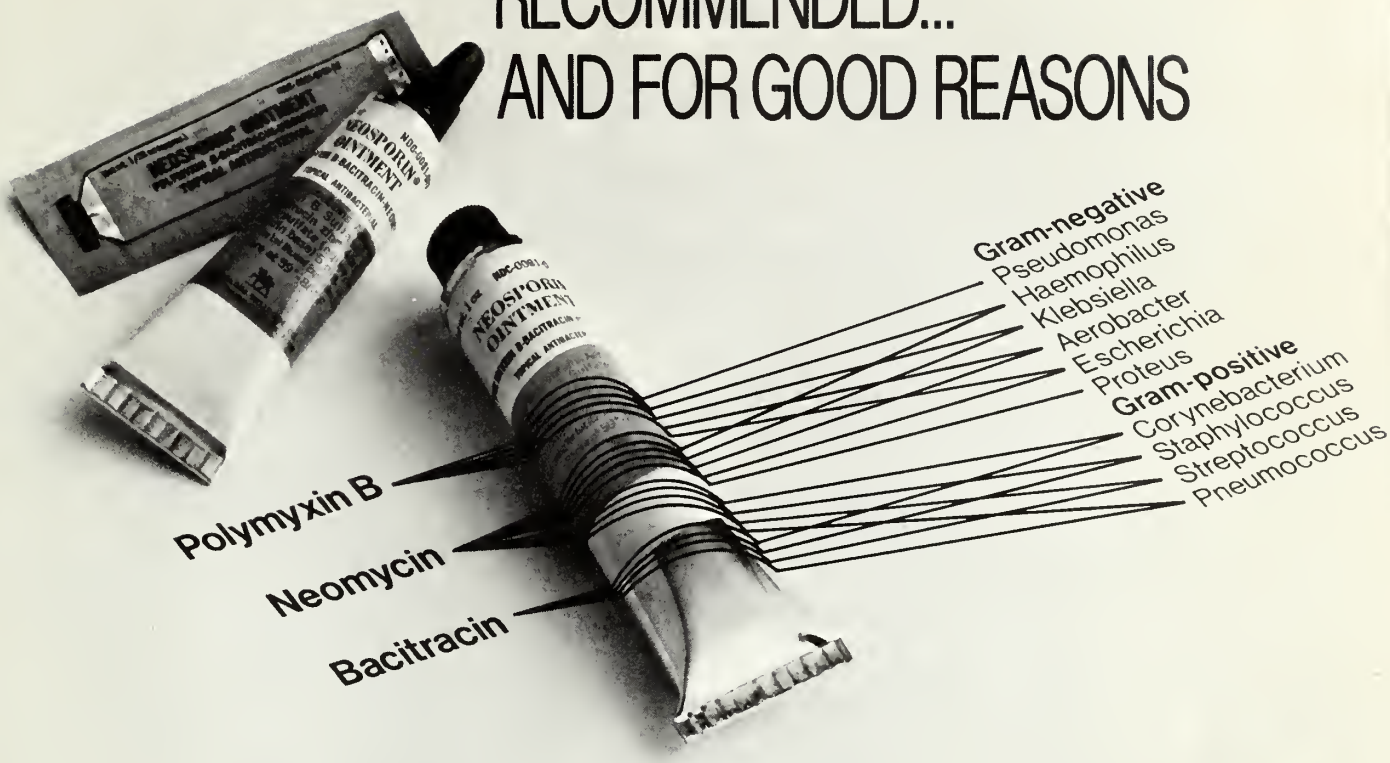

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ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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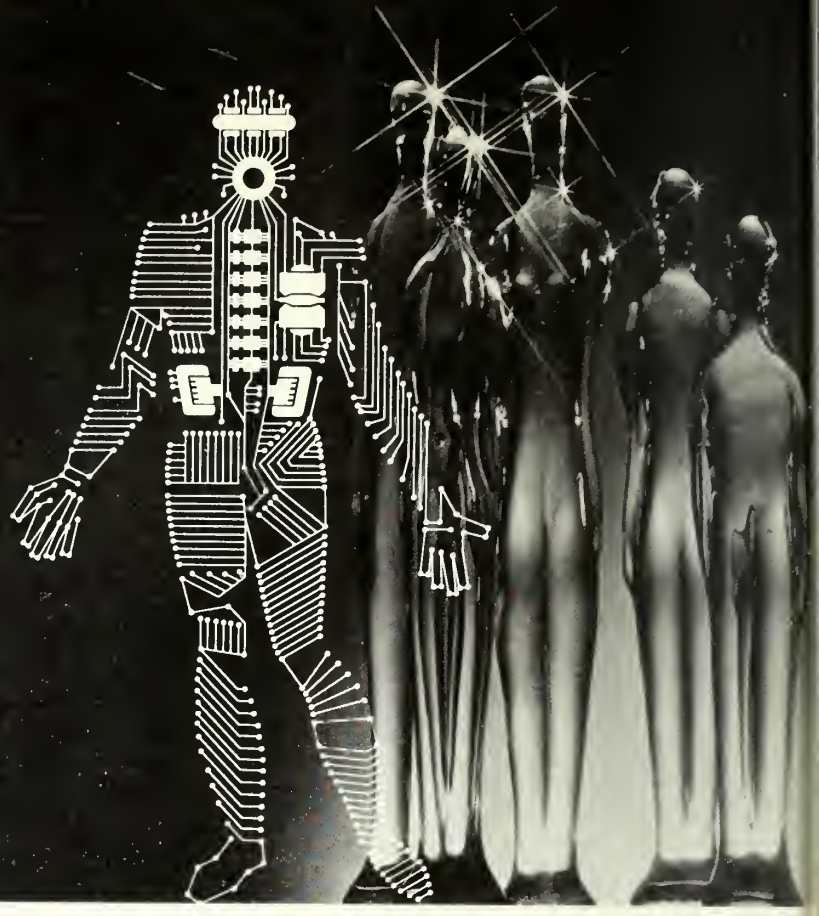

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The usual starting dose of Catapres is 0.1 mg at breakfast and 0.1 mg at bedtime. Some patients may benefit from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg
Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1, 0.2, 0.3 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.
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Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances, anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months

Precautions: In depression accompanying anxiety, consider possibility for suicide

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions

Observe usual precautions with impaired renal or hepatic function

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown, but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease

Safety and effectiveness in children under 12 years have not been established

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia, some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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Why one benzodiazepine and not another?

Are you concerned about long-acting metabolites? Many clinicians, as well as pharmacologists, are beginning to draw attention to this problem (see New England Journal of Medicine, April 5, 1979).

In contrast to some older benzodiazepines, Ativan (lorazepam) does not give rise to long-lasting active metabolites. As with all benzodiazepines, you should follow the usual precautions concerning co-administration with other CNS depressants and warn your patients against operating dangerous machinery and motor vehicles.

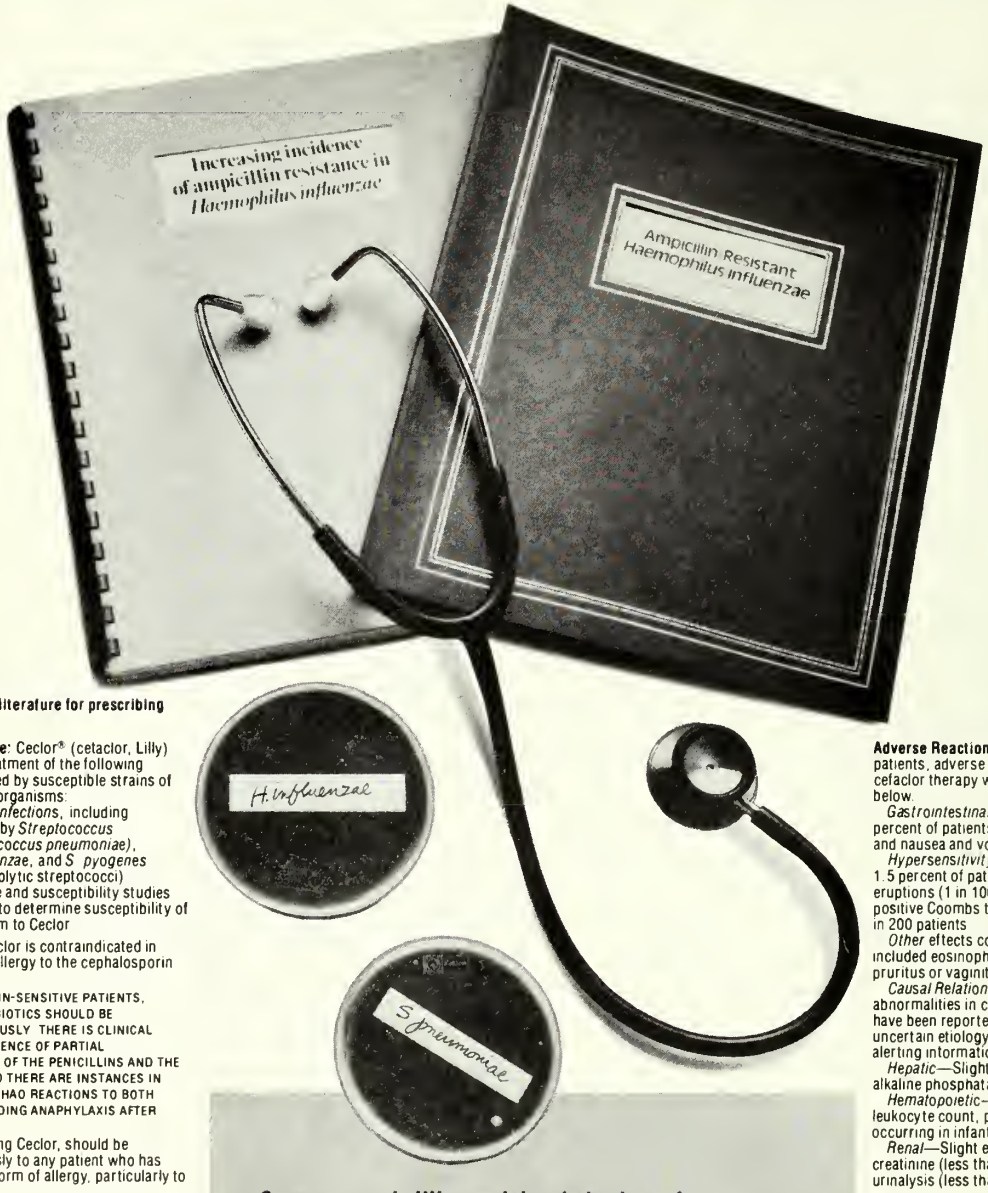
However, it is noteworthy that Ativan showed no clinical evidence of accumulation even when given in high doses over periods up to 6 months. The half-life of free lorazepam is about 12 hours; steady-state serum levels are attained in 2-3 days. Comparable data for diazepam: 20-50 hours and at least 7-10 days. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Ativan has a convenient b.i.d. or t.i.d. dosage schedule; it is compatible with a long list of other medications and, of course, it is a highly effective anxiolytic agent, as established in numerous nationwide, double-blind, controlled evaluations in thousands of patients.

See important information on preceding page.

Ativan® (lorazepam) **for Anxiety**

An added complication... in the treatment of bacterial bronchitis*



Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below.

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory tests results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [070379R]

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.*

Note. Ceclor® (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

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THE WESTERN
Journal of Medicine

Refer to: Clark OH: Thyroid nodules and thyroid cancer: Surgical aspects. West J Med 133:1-8, Jul 1980

Thyroid Nodules and Thyroid Cancer: Surgical Aspects

ORLO H. CLARK, MD, *San Francisco*

Patients with thyroid nodules must be treated selectively because these nodules develop far more frequently than does thyroid cancer. A thorough clinical history, family history and history of radiation, as well as an accurate physical examination, are very important in determining whether surgical treatment is indicated. Thyroid function tests, a radioactive isotope scan, a thyroid echogram and fine-needle biopsy are also useful.

Although there is considerable debate concerning the amount of thyroid tissue that should be removed at operation, the minimal procedure for a "cold," solid thyroid nodule is a total thyroid lobectomy and isthmectomy. This is the treatment of choice for patients with occult papillary thyroid carcinoma. Partial lobectomy is to be discouraged. Near total or total thyroidectomy should be considered for all other patients with differentiated thyroid cancer.

Many factors influence the prognosis of patients with thyroid cancer including age, sex, type of thyroid cancer, invasion, symptoms, lymph node metastasis, metastasis to distant sites, extent of the surgical procedure, and use of radioactive iodine and thyroid hormone. With adequate treatment, the prognosis for differentiated thyroid carcinoma is excellent.

THE OCCURRENCE OF thyroid cancer is increasing, and considerable debate exists over the selection of patients with thyroid nodules for thyroidectomy and how much thyroid tissue should be removed at operation.[1-3] Patients with thyroid nodules must be treated selectively. While about 4 percent of persons in the United States have thyroid nodules, only .004 percent or 40 persons per million have thyroid cancer, and only 6 patients per million die of this disease.[4-6] The variable and generally prolonged course of thyroid cancer, the hormone dependence of many thyroid tumors and the wide spectrum of neoplasms with varying biologic characteristics, make the evaluation and interpretation of various methods of treatment difficult.

Evaluation of Patients

This paper presents a logical approach to the diagnosis and treatment of patients with nodular goiter. Clearly, the main concern when evaluating a thyroid nodule is whether the nodule is malignant. Observation alone, without surgical intervention, is appropriate in some patients: those with diffusely enlarged goiters or multinodular

From the Department of Surgery, Veterans Administration Medical Center, and the University of California, San Francisco.

Submitted, revised, October 18, 1979.

This work was supported in part by the Medical Research Service of the Veterans Administration.

Reprint requests to: Orlo H. Clark MD, 400 Parnassus Ave., Rm 680-A, University of California Medical Center, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

goiters without a dominant lesion, with high antithyroid antibody titers, with a family history of benign goiter or with nodules that disappear after treatment with an exogenous thyroid hormone. However, young patients with thyroid nodules, patients with "cold," solid thyroid nodules or nodules that are growing, those who have received radiation therapy, and those with nodules, in whom hoarseness, dysphagia, cervical adenopathy or a hard fixed thyroid mass has occurred, must be considered candidates for operation.[7,8] Thyroid cancer also occurs in patients with multiple endocrine adenomatosis type II or the Sipple syndrome (medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism).

All patients with thyroid nodules should be evaluated for any localized or systemic symptoms, and their thyroid function determined. Virtually all adult patients with a clinically solitary or dominant thyroid nodule should have a radioactive iodine (iodine 123) scan. The scan helps confirm the accuracy of the clinical examination, determines whether the lesion is solitary or multiple and whether it is nonfunctioning ("cold") or functioning ("warm" or "hot"). Multinodular goiters have a lower incidence of thyroid cancer than solitary nodules. Hot nodules detected by radioactive iodine scan are rarely malignant, but may cause hyperthyroidism, whereas cold solitary thyroid nodules have a 20 percent chance of being malignant[7] (Figure 1). A ^{123}I or technetium 99m scan using a gamma (scintillation) camera with a pinhole collimator is also recommended for all patients who have received 6.5 or more rads to the thyroid as children or as young adults, because thyroid nodules may be missed on physical examination. Also, as little as 6.5 rads to the thyroid gland is associated with a sixfold increase in thyroid cancer when compared with siblings who have not undergone radiation therapy. Thyroid

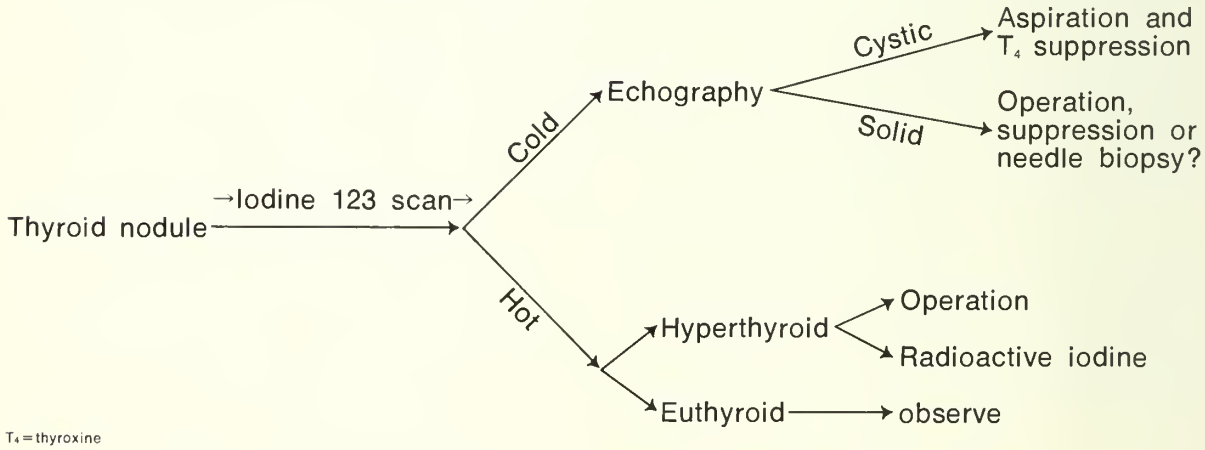

Figure 1.—Recommended method of evaluating a patient with a thyroid nodule.

TABLE 1.—*Thyroid Lesions After Irradiation**

Area or Type of Treatment	*Estimated Dose to Thyroid (Rads)*	*Incidence (Percent)*		*Source*
		Nodular Goiter	*Cancer*	
Scalp	6.5	..	0.11	Modan et al[10]
Thymus				
Total group	119	1.8	0.8	Hempelmann et al[11]
Subgroup	399	7.6	5.0	
Neck, chest	807	27.2	5.7	Favus et al[12]
	180-1,500	26.2	6.8	Refetoff et al[13]
Radiation fallout	175(γ) and 700-1,400 (β)	39.6	5.7	Conard et al[14]
^{131}I therapy	±10,000	0.17	0.08	Dobyns et al[15]

*Adapted from Greenspan FS: Radiation exposure and thyroid cancer. JAMA 237:2089-2091, 1977

TABLE 2.—*Diagnostic Radioactive Pharmaceutical Examinations and Estimated Dose to the Adult Thyroid Gland**

Radioactive Pharmaceutical Agent and Type of Examination	*Estimated Dose to Adult Thyroid (Rads)*
^{123}I thyroid scan	2.8
^{123}I thyroid uptake	6.0
^{131}I thyroid uptake	10.5
^{131}I thyroid scan	100-200
^{99m}Tc thyroid scan	0.1

*Adapted from Silverman C, Hoffman DA: Thyroid tumor risk from radiation during childhood. Prevent Med 4:100-105, 1975

cancer has also been reported to occur in 22 of 62 patients (35.5 percent) in whom scans showed abnormalities but physical examinations did not.[9] Multiple radioactive iodine scans are not recommended unless cancer has been discovered.

Table 1 shows the relationship between the dose of radiation administered and the development of thyroid disease. The radiation dose most likely to induce thyroid cancer is approximately 1,500 rads. However, as little as 6.5 rads to the thyroid gland, received during the course of radiation of the scalp for tinea capitis, resulted in a sixfold increase in thyroid cancer: 0.11 percent in treated patients compared with 0.02 percent in untreated siblings. In dose ranges of 400 to 1,500 rads, the incidence of nodular goiter was about 27 percent to 40 percent, whereas the incidence of thyroid cancer varied from 5 percent to 9 percent. With larger doses of thyroid radiation, the incidence of malignant neoplasms seems to decrease but the incidence of hypothyroidism increases.

The amount of radiation that the thyroid receives from the various thyroid scans is summarized in Table 2. The absorbed radiation dose to the thyroid depends on the following: amount administered, type of radioactive isotope, percent uptake, size of thyroid gland, age of subject and route of administration. Thyroid-absorbed doses vary greatly with age—they are lowest in adults (20 years of age and older), progressively higher in children, and in newborns may be more than 20 times the adult dose.

If a thyroid lesion is cold, thyroid echography is recommended. Approximately 15 percent of the cold nodules are cystic, and *cysts* of the thyroid are rarely malignant.[16,17] However, metastatic thyroid cancer in regional nodes is frequently cystic.[18] If the thyroid nodule is cystic by echography, then treatment by aspiration is safe and makes operative removal unnecessary in about 70 percent of patients because the lesion either disappears or dramatically regresses leaving a minimal residual lesion.[18]

Fine-Needle Biopsy

Fine-needle biopsy of solid thyroid nodules also seems valuable in selected patients. Biopsy is not recommended in patients who have previously received radiation treatment because of the multifocal nature of these tumors.[19] Needle biopsy is (1) safe and provides additional diagnostic material, (2) reliable for Hashimoto thyroiditis and undifferentiated thyroid tumors and (3) as accurate as frozen section (approximately 80 percent) for thyroid nodules.[20-22] Needle biopsy also rarely gives false-positive diagnostic information and needle tract implantation is rare.[23] To my knowledge there has been no documented case of local tumor extension in the needle tract following fine-needle (18- to 22-gauge) biopsy. The main limitations of percutaneous needle biopsy include false-negative diagnosis because of incorrect location of sampling[24] and the inability to distinguish between a well-differentiated follicular carcinoma and a highly cellular benign follicular adenoma.[23] As long as the clinician and patient are aware of these limitations and biopsy is viewed as an additional diagnostic aid to the history and to physical and laboratory findings, then percutaneous biopsy is useful for evaluating thyroid nodules. Close cooperation with a competent anatomic pathologist or cytologist is essential for biopsy to be helpful.

Factors Influencing Survival

Factors that influence prognosis in patients with thyroid cancer are age, sex, type of thyroid cancer, size of the tumor, invasion, symptoms, lymph node involvement, metastasis to distant sites, extent of surgical operation, use of radioactive iodine and exogenous thyroid hormone therapy.[3,25-27]

Virtually all studies concerning differentiated thyroid cancer show that patients younger than 7 or older than 40 years of age are more likely to die of this cancer than those between 8 and 39 years.[8] This is in spite of the fact that the recurrence of cancer is more common in younger persons. Women have a greater incidence of thyroid cancer than men, but men have a worse prognosis. Women also have more benign thyroid nodules than men, therefore any given thyroid nodule is more likely to be malignant

in a man than in a woman. Although most forms of thyroid cancer are not symptomatic, those which cause pain, hoarseness, dysphagia or grow rapidly have a more ominous prognosis and usually represent either dedifferentiation to undifferentiated lesions or anaplastic tumors. Large tumors (more than 2.5 cm in size), invasive tumors and those that have metastasized to distant sites also adversely influence survival. Whether or not lymph node metastasis influences survival is controversial.[28-31] Studies from the Lahey Clinic suggest that lymph node metastasis may be beneficial.

Because numerous investigations have shown that microscopic thyroid cancer is present in approximately 75 percent of patients undergoing prophylactic neck dissections (and who had no grossly perceptible lesions),[32-33] I believe that lymph node metastasis indicates the presence of more cancer. At the University of California, San Francisco, when patients with and those without nodal metastasis were matched for age, the presence of nodal metastasis signified a poorer prognosis. It should be mentioned, however, that lymph node metastasis is most common in the young, with as many as 80 percent of children having clinically positive nodes at the time of diagnosis.[34] Only about 20 percent of patients older than 30 years have metastatic disease.[34] Even so, children with nodal metastasis still have an excellent long-term prognosis.[31-34]

Thyroid Pathology

Obviously, the type of thyroid cancer is important in predicting survival. Primary thyroid tumors generally may be separated into benign (adenoma, cyst, localized thyroiditis) and malignant categories, but in some instances the distinction is difficult. The types of adenoma include follicular, embryonal, atypical, Hürthle cell and papillary (although some observers consider all papillary tumors to be a form of carcinoma). The types of malignant tumors are given in Table 3.

For atypical adenomas a minimum of eight satisfactory histologic blocks, including the capsule, should be surveyed to rule out invasion of the capsule. *Occult* papillary carcinomas (1 cm or less in size) have a very favorable prognosis. In fact, if an occult tumor is removed in the course of a thyroidectomy done for another reason, it should be considered as an incidental finding that requires no additional surgical treatment. Occasionally, widespread metastatic lesions may occur with an occult primary carcinoma. When cervical lymph nodes contain metastatic thyroid cancer (lateral aberrant thyroid) and no lesion is palpable in the thyroid gland, the occult papillary cancer is virtually always in the ipsilateral lobe of the thyroid gland. Psammoma bodies are frequently found (60 percent to 70 percent) in papillary thyroid cancer and rarely found in follicular thyroid cancer, but they are of no prognostic significance.[35] Papillary carcinoma, which accounts for about 60 percent to 80 percent of cases of thyroid cancer, has the most favorable prognosis; follicular carcinoma (20 percent to 30 percent) has a slightly poorer prognosis, and undifferentiated or anaplastic carcinoma (1 percent to 5 percent) has a dismal prognosis. Life expectancy in patients with differentiated (papillary, mixed-follicular and follicular) carcinoma is usually compared at 15 years, whereas 80 percent to 90 percent of patients with undifferentiated thyroid carcinoma are dead within a year. Medullary carcinoma has an intermediate prognosis between the differentiated and undifferentiated types (Figure 2).

TABLE 3.—*Malignant Tumors of the Thyroid Gland*

Differentiated carcinoma
Papillary (60%-80%)
Occult
Pure papillary
Mixed papillary-follicular
Follicular (20%-30%)
Encapsulated or slightly invasive
Invasive
Undifferentiated carcinoma (10%-15%)
Anaplastic, squamous cell, spindle cell, giant cell, small cell
Medullary (1%-5%)
Other (1%-5%)
Lymphoma
Fibrosarcoma
Malignant teratoma
Malignant mixed tumors
Metastatic tumors

Extent of Surgical Intervention

There is considerable controversy about the extent of surgical intervention for thyroid cancer. Virtually all clinicians agree, however, that the minimal operation for a solitary thyroid nodule is a thyroid lobectomy and isthmectomy on the side of the nodule.[26,27] If the nodule is situated in the isthmus, resection of the isthmus along with the anterior third of each lobe is usually recommended. If frozen section shows the lesion to be benign then the operation is completed. If

malignant, more tissue should be removed. Factors influencing the amount of thyroid tissue to be removed include (1) type of cancer, (2) involvement of the contralateral lobe, (3) metastasis, (4) experience and prejudice of the surgeon, (5) intelligence and reliability of the patient and (6) history of radiation exposure to head and neck. Obviously, if there is bilateral involvement of the thyroid gland with cancer, a near total thyroidectomy (preserving the posterior lateral capsule on the side of the neck with less tumor) or total thyroidectomy should be done, regardless of whether the tumor is papillary, follicular or medullary. Cutting through gross tumor increases the chance of tumor recurrence and shortens survival.[3,26] The rate of recurrence within the thyroid in these patients ranges from 30 percent to 50 percent.[6]

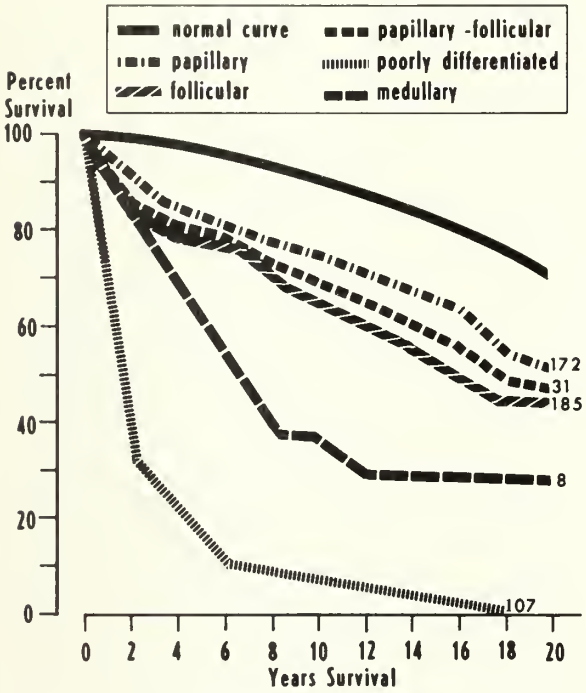

Figure 2.—Survival curves for several types of thyroid cancer. Normal population from interpolation of the Abridged Life Tables. Numbers indicate number of patients. (Data from Buckwalter JA, Thomas CG Jr: Selection of surgical treatment for well differentiated thyroid carcinoma. Ann Surg 176:565-578, Oct 1972.)

TABLE 4.—*Reasons for Total Thyroidectomy*

- As many as 87.5 percent of patients have microscopic cancer in the contralateral lobe.
- In approximately 7 percent to 10 percent of patients recurrent clinical cancer in the remaining lobe develops.
- Half of the patients in whom recurrent thyroid cancer develops die of this disease.
- A fourth to a half of the patients who die of thyroid cancer do so because of unresectable central neck disease.
- The chance of a differentiated thyroid cancer becoming an anaplastic thyroid cancer, which occurs in approximately 3 percent to 5 percent of cases, becomes less likely.
- Follow-up with radioactive iodine scanning is easier to evaluate for disseminated disease.
- Thyroglobulin can be used as a tumor marker for metastatic differentiated thyroid cancer because serum levels should be negligible in patients after total thyroidectomy.

Near total thyroidectomy is the operation done most commonly in the United States for the treatment of papillary carcinoma.[6] Some investigators favor a total or near total thyroidectomy for all papillary, follicular and medullary thyroid cancer except for localized occult cancer, in which the prognosis with lesser procedures is excellent. This approach must be used with some reservation because a lobectomy has been shown to be an acceptable means of treating papillary thyroid cancer grossly confined to one lobe, and offers a prognosis of long-term survival comparable with that of more extensive operations.[26] If the incidence of permanent hypoparathyroidism is higher than 1 percent after total or near total thyroidectomy, then less than a total thyroidectomy should be done. Reasons for total thyroidectomy are listed in Table 4.

Unfortunately, most forms of undifferentiated thyroid cancer are unresectable at time of operation. Therefore, generally the surgical goal is to obtain tissue for histological examination so that radiation therapy can be given.[36]

Neck Dissection

Papillary and some follicular carcinomas spread via the local lymphatic channels. A modified radical neck procedure is recommended in these patients when lymph nodes are clinically involved. Several studies suggest that survival and recurrence rates are similar in patients treated by either a standard radical or a modified radical neck dissection.[6,37] Prophylactic neck dissections are not recommended for papillary and follicular thyroid carcinoma because, despite the fact that tumors may be discovered in about 75 percent of these patients, the tumors recur in only about 10 percent of them. Delay in removal of lymph nodes until they become palpable does not appear to influence survival.[3,38,39] A modified neck dissection using an en bloc procedure is recommended rather than "berry picking" because

whenever a node larger than 3 mm contains thyroid cancer, cancer will always be found in the smaller lymph nodes.[33] During an en bloc dissection, however, the spinal accessory nerve, sternocleidomastoid muscle and internal jugular vein are preserved unless the tumor is locally invasive. Transverse incisions are recommended because they provide a better cosmetic result and heal faster than vertical incisions.

If the voice is normal (and vocal cords moved normally before the operation) and the recurrent laryngeal nerve is found to be surrounded by tumor at operation, the nerve usually can be dissected free from the tumor with preservation of function. This is best accomplished by identifying the nerve caudad to the tumor. Lymph nodes that frequently extend into the anterior superior mediastinum usually can be removed via the cervical incision, as indicated by the experimental studies of Chouke and co-workers.[40] They observed a lack of communication between lymphatic channels in the anterior or superior mediastinum and those in more inferior mediastinal levels.

In cases of medullary thyroid cancer, prophylactic neck dissections and, frequently, standard radical neck dissections are recommended. Some patients who have had total thyroidectomies for medullary cancer, but who have no clinical evidence of metastasis, may be evaluated for residual tumors by provocative tests (calcium or pentagastrin infusion) to determine if calcitonin levels have increased.[41-43] If residual medullary cancer is present, serum and urine calcitonin levels will increase in response to infusion of calcium or pentagastrin.[42,43]

Postoperative Management

Following total thyroidectomy for papillary and follicular cancer, the patient is usually given a dosage of 25 μg of liothyronine sodium (Cytomel) orally three times a day. After three months, when the patient has been reassured and his surgical wound is completely healed, this medication is discontinued for two weeks and the patient is given a scanning dose (1 mCi) of iodine 131. Liothyronine (triiodothyronine or T_3) is used postoperatively for thyroid hormone replacement rather than thyroxine (T_4) because it has a half-life of about a day, whereas T_4 has a half-life of about a week. Thus, one can be assured that by two weeks after discontinuing T_3, serum thyroid-stimulating hormone (TSH) levels will be substantially elevated. If there is no radioactive iodine uptake in the neck or elsewhere in the body, the patient's medication is changed to about 0.2 mg of levothyroxine sodium per day. Serum thyroglobulin determination is a useful marker for metastatic differentiated thyroid cancer and is most sensitive when the patient is hypothyroid, that is, just before his scan, because a TSH test is an excellent provocative test for thyroglobulin.[44,45] If the thyroglobulin is positive, then persistent disease should be suspected.[46] If negative, persistent or recurrent tumor is less likely.

If there is uptake of radioactive iodine in the lateral portion of the neck suggesting nodal metastasis, this area should be carefully examined. If lymph nodes are palpable, a modified radical neck dissection should be done. If no nodes are palpable but there is uptake of radioactive iodine, treatment with ^{131}I is recommended. Unfortunately, ^{131}I is not especially effective in treating palpable metastatic nodes but is effective for microscopic functioning metastastic lesions. Wilson and Block[37] reported that treatment with ^{131}I was helpful in only 50 percent of patients with papillary thyroid cancer that metastasized to regional lymph nodes and in none of the patients with follicular carcinoma. External radiation was even less effective in these patients because in all those with either papillary or follicular cancer and nodal involvement tumors recurred. The rates of recurrence in patients similarly treated by a modified neck dissection was 21 percent, and after standard radical neck dissection 29 percent. Although external radiation is generally not effective in treating nodal metastasis, it is useful in patients with metastatic thyroid cancer that does not take up radioactive iodine. It is also useful for treating invasive cancer left in the thyroid bed.[47] Patients treated by thyroidectomy, radioactive iodine and thyroid hormone to suppress TSH, have been reported to have a lower incidence of tumor recurrence.[3]

Prognosis

Thyroid cancer is more lethal than is commonly thought by many clinicians.[48] About 19 percent of 554 treated patients reported by Ibanez and co-workers[49] and 32 percent of 685 patients reported by Woolner and associates died of this disease.[50] Anaplastic thyroid cancer resulted in earlier death due to extensive local and disseminated disease while papillary and follicular cancer were associated with a more protracted course. About a fourth of the latter patients died of local

extension of tumor and the remainder from metastasis to local nodes, lungs, bone and elsewhere.

Suppression of TSH and Adjuvant Therapy

Thyroid hormone should be given for two reasons to all patients who have had thyroid resections for cancer. First, in most cases much of the gland has been removed so thyroid hormone is given to keep the patient euthyroid. Thyroid hormone should also be given to suppress TSH levels. Studies in animals have shown that the development of some forms of thyroid cancer can be prevented by suppressing TSH.[51,52] Several retrospective studies have indicated that recurrence of cancer is minimized and survival dramatically improved in patients treated with exogenous thyroid hormone.[3,37,53,54] We and others[55-57] also have reported that differentiated malignant thyroid tumors have TSH receptors. These tumors also respond metabolically in vitro to TSH stimulation.[55,56,58-60]

The amount of exogenous thyroid hormone required to suppress tumor growth is unknown. Serum TSH levels should be measured periodically to see that they remain suppressed. If there is any question about the proper amount of thyroid hormone, a thyrotropin-releasing hormone (TRH) test may be useful. The lowest dose of thyroid hormone that inhibits the response of serum TSH to TRH should be used.

Chemotherapy is indicated for patients with thyroid cancer that is unresponsive to surgical intervention, TSH suppression or radiation therapy. Generally, these patients have either undifferentiated tumors or recurrent local or disseminated differentiated cancer that has not been successfully treated by an operation and radiation therapy. Approximately 35 percent of patients with uncontrolled thyroid cancer have a partial remission with subjective improvement when treated with doxorubicin hydrochloride (Adriamycin) in a single injected dose of approximately 75 mg per m^2, or divided into three consecutive daily injections that are repeated at three-week intervals. Toxicity may include cardiotoxicity, myelosuppression, leukopenia, thrombocytopenia, alopecia and gastrointestinal problems.[61,62]

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Weight Loss as Determinant of Diuretic Therapy

BODY WEIGHT is the easiest and most accurate way to determine how diuretic therapy is proceeding. . . . Because the fluid from edema can be instantly mobilized into the circulation, if you give a hefty dose of furosemide, and get a prompt diuresis, you will not put the patient into shock. Therefore, the mobilization of this fluid will prevent a catastrophic event.

The problem is that when you see these patients, and they have even massive ascites but very little or no edema—these circumstances are really time bombs. You have to be very careful when you promote a diuresis in these patients. . . . Studies have shown that ascites can be mobilized from the peritoneal cavity at a rate of 900 ml per day. That means you can put the patient in complete shock, but the fluid is going to leave that peritoneal cavity at a maximum rate of 900 ml per day. Therefore, you really have to adjust your diuretic therapy so you do not have the patient losing any more than this amount of fluid per day. If you have ascites plus edema, you should probably aim for a weight loss about 1 kg per day, with diuretics. If there is no edema, you have to be much more careful and you probably have to stay under 0.5 kg of weight loss per day.

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A Biopsychosocial Approach to Surgical Evaluation and Outcome

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There is increasing necessity for including an evaluation of psychosocial as well as biomedical factors when assessing the need for surgical intervention and its possible outcomes. Potential problems between patient and surgeon can arise when these factors are not taken into account. Recent behavioral science literature supports the use of a conceptual framework and concise clinical method for evaluating psychosocial factors and negotiating treatment with a patient. Such a method may be useful in reducing patient-surgeon conflicts and the negative outcomes (such as patient noncompliance, dissatisfaction, medical-legal suits and poor patient care) that can result when such an assessment is not mutually discussed.

THE PROCEDURES USED to evaluate the need for an elective surgical procedure and its outcome are based primarily on criteria determined by physicians—that is, on physiological and biomedical evidence.

However, recent literature has indicated the importance of recognizing the individual and personal view of illness held by a patient in determining the course of illness and therapeutic outcome and, especially, in minimizing differences in patient and physician evaluations of successful health care.[1,2]

Evaluation of Surgical Outcome

Several studies have shown that a patient's perceptions of an unsuccessful surgical operation may be determined more by psychosocial than by physiological and biomedical evidence of failure.[3-5] Peptic ulcer operations are a prime example of this dichotomy in evaluating surgical outcome. Several criteria formulated by physicians to measure the outcome of the operation include acid reduction, absence of diarrhea, ulcer recurrence and loss of weight. Kay and Phillips[3] collected follow-up data on 500 patients seen after this operation and found that the current methods of assessing a successful outcome for a peptic ulcer operation were inadequate. That is, "satisfactory results in the eyes of the surgeon may be regarded as a failure by the patient." They measured each patient's perception of his or her quality of life after the operation by using a questionnaire that included issues such as sleep, recreation, social life, family relationships, work and sexual activity, as well as questions about the usual physical symptoms that occur after a gastrectomy, such as vomiting, diarrhea, dumping, weight loss and distention. They recommended that the criteria determining a patient's style and quality of life should be monitored before the operation to adequately assess which patients should be treated with surgical as opposed to medical management. Again, doctor-determined criteria alone would not be adequate to assess the need for surgical intervention.

Another example of inadequate evaluation screening before the surgical procedure as well as inadequate evaluation of postoperative results is in disk operations in patients with lower back pain. A surgeon's preevaluation tests are based primarily on a physical examination (the quality

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and intensity of the pain and whether it follows a nerve root distribution to the legs) and a myelogram. Postoperative results are often measured by the degree of pain that still exists, as well as by myelogram findings. Pondaag[4] presented results that indicated that a battery of psychological tests accurately predicted positive outcome of disk operations about 94 percent of the time and an unfavorable outcome about 77 percent of the time. This study clearly indicates the inadequacy of evaluating patients for disk operations as well as for possible postsurgical results solely on a biomedical basis.

"Illness" Versus "Disease"

Several social scientists[5-8] who are clinically oriented have published ideas congruent with those above with regard to assessing illness problems. They have pointed out that a patient's chief concern is "illness"—that is, his or her perceptions of the personal and social significance of the illness as well as the problems created by the experience of it. On the other hand, clinicians schooled in the biomedical paradigm are chiefly concerned with "disease"—that is, malfunctioning and maladaptation of biological or psychological processes, or both. Therefore, doctors socially construct sickness as disease while patients construct sickness as illness. To go a step farther, patients frequently evaluate the outcome of treatment in terms of successful management of illness problems (such as the provision of personal and social meaning and the resolution of life stress) rather than whether the disease itself has been cured. Physicians search for technical treatments to control or cure the actual disease, and evaluate outcomes principally in these terms.

Once again, the case of peptic ulcer disease is illustrative. It is possible to define peptic ulcer disease (by doctor-determined criteria) as a disease whose symptoms are caused by a mucosal lesion and whose symptoms disappear when the ulcer heals.[9] However, a recent report[10] pointed out that although a regimen of high-dose antacids healed the ulcers of 78 percent of the patients in a group receiving "active medicine" as compared with 45 percent of a group receiving placebos (in a double-blind study carried out with direct gastroscopic monitoring), at the end of four weeks there was no difference between them in symptomatic outcome. Both groups had a substantial reduction in symptoms. Even more striking, half of the patients with persistent ulcers became asymptomatic. The authors concluded that the "loss of ulcer symptoms did not guarantee ulcer healing or even decrease in size." Therefore, a patient may consider himself cured because his symptoms remit, while the doctor remains dissatisfied because the ulcer is unchanged. Or a physician may consider treatment successful because the lesion (that is, the disease) has been cured, while the patient considers himself ill because his symptoms persist.

The case report below exemplifies both an inadequate biomedical assessment of illness problems before surgical intervention and an equally inadequate postoperative assessment of outcome. This case illustrates the conflicts that can arise between surgeon and patient because of differences in belief and value systems.

In our discussion of this case we will present a crucial method for patient management, aimed at resolving the previously mentioned problems, that should be an essential part of surgical care. Studies in the health services field have shown that this type of intervention may positively affect compliance, patient satisfaction, and possibly medical-legal suits.[11-16]

Report of a Case

The patient was a 42-year-old woman in whom an intestinal bypass surgical operation had been done 16 months earlier. She was brought to the Harborview Medical Center, Seattle, after taking an overdose of a sedative hypnotic drug. She had a history of obesity since early childhood, as well as a strong family history of extreme obesity, with her mother weighing 400 pounds, her sister 400 pounds and her father 700 pounds. The patient stated that she had been happy at her previous weight of 350 pounds, but due to constant pressure by her doctors, friends and peer group, she had decided to undergo the intestinal bypass operation. The only physical problem she had secondary to obesity was mild hypertension (in the range of 140/90 mm of mercury).

The patient stated she had devoted much of her life to proving that obese people could do most of the things that thin people could do, such as swim, water ski and hike. She had been exceedingly active, raised three children on her own after a divorce and worked regularly as a vocational nurse. Before the operation she had lived with a man for two years. She said that there were no significant problems in their relationship. Fin-

ally, 16 months before admission, at age 40 she decided to have the intestinal bypass operation.

The technical results of the bypass were good. The patient lost 100 pounds, her surgical wound healed well and her blood pressure decreased. However, the side effects of the procedure and resulting illness problems were considerable.

She began having 10 to 12 bowel movements per day, had occasional fecal incontinence and problems with flatulence. She was admitted to hospital four times due to syncope and orthostatic hypotension. Before the operation she had described herself as jovial, often the center of attention, hardworking and enjoying her primary relationship with her boyfriend. After the operation and resulting symptoms she had problems with her body image. She felt that the doctors had taken away a third of her body and that she was no longer a complete person.

The patient said that she had insomnia and decreased energy, and had been having suicidal ideas for many months before taking the overdose. She had begun to miss work frequently because of the side effects of the operation, had financial problems due to the recurrent hospital stays, and her depression and irritability had started to cause problems with the man she was living with.

She visited at least five surgeons before taking the overdose. She was gradually more insistent that they reanastomose her bowel. All refused, however, stating that the operation was successful —that is, she had lost 100 pounds and her blood pressure had decreased. They offered to try to control her side effects with medication. Finally, in desperation, the patient decided that she no longer wished to live with her physical problems and her perception of a substantial decrease in the quality of her life. Thus, she took an overdose of sedative medication.

Discussion

The literature on the psychosocial sequelae of intestinal bypass operations for obesity has been controversial regarding the degree of morbidity in these patients.

A recent literature review by Solow[17] reported that in most patients the psychosocial results were positive, including improvement in activity level, mood, self-esteem, and interpersonal and vocational effectiveness, as well as a trend toward normal eating behavior. However, both Solow[17] and Castelnuovo-Tedesco[18] emphasize that if the procedure induces severe physiological side effects, even the patients who were the most psychologically competent before surgical therapy will be unhappy with the outcome.

The above case is illustrative of differences between surgeons and patients in evaluating the outcome of an operation. If a physiological and biomedical approach is used—that is, that the patient had (1) lost 100 pounds, (2) become normotensive, (3) experienced no severe postsurgical complications and had normal wound healing, and (4) suffered a malabsorption syndrome that was an expected physiological result of the operation which led to unpleasant but not life-threatening side effects, then the operation appeared successful. The orthostatic hypotension, hyperphagia, fecal incontinence, constant diarrhea and flatulence were undesirable but understandable side effects of a procedure that potentially might have a major benefit in the development of the patient's future health status. Based on only the above data, the surgeons involved might well decide that despite the side effects from the operation, the patient had received many benefits and conservative medical management would seem appropriate from here on. Her surgical procedure would be given a positive evaluation, as had been done by the surgeons who were actually involved with the case.

Yet, when we look at the events from the patient's perspective, the outcome looks entirely different. To elicit such patients' perspectives of their surgical outcome and the biopsychosocial problems that may result from the procedure, we developed a three-step clinical method. This method can be used (1) to evaluate whether a patient should have an operation, (2) to assess possible surgical outcomes and (3) to assist in the routine clinical care of patients. Indeed, we have successfully taught this method to primary care physicians.

As our patient described her perspective of her surgical outcome it was obvious that her evaluation of the procedure contrasted strikingly with that of her physicians. Further, her viewpoint had not been taken into account, and the "hidden" conflict led to her inability to cope with her condition and to her attempted suicide.

Clinical Method for Biopsychosocial Evaluation of Surgical Patients

Step 1

Step one (called the patient's explanatory model) involves the surgeon asking the patient to

TABLE 1.—*Possible Illness Problems to be Assessed in a Comprehensive Approach to Surgical Care*

- Maladaptive coping responses that patients and families use to manage sickness, such as denial, passive-hostile behavior, "shopping" among different doctors, and suicidal attempts.
- Financial problems created or worsened by sickness.
- Family problems created or worsened by sickness.
- Major changes in a person's social role resulting from a terminal sickness or a permanent disability.
- Inappropriate resort to a sick role and illness behavior owing to psychological or social gain.
- Conflict in personal beliefs between patient (and family) and practitioner(s) concerning course or nature of sickness and objectives for treatment.
- Conflict in cultural values concerning treatment style and interpersonal etiquette between patient and practitioners due to substantial differences in social class, life-style and ethnic norms.
- Lack of patient compliance with therapeutic regimen due to the unusual nature of a procedure or its expected outcome.
- Inappropriate use of alternative or indigenous health care agents and agencies.
- Breakdown in communication between patient (and family) and practitioner(s).
- Special life problems stemming from the stresses engendered by the treatment environment.

describe (1) his or her illness or what is wrong, (2) expectations about type and style of treatment and (3) what goals should be considered as effective care. The clinician should first ask the patient general, open-ended questions about his or her view of the sickness. If this does not elicit the necessary information (and it frequently will not), then the clinician should inquire specifically about the patient's beliefs concerning each of these five issues: (1) cause of the illness, (2) reasons for the onset of symptoms at a particular time, (3) pathophysiology, (4) course (severity and type of sickness role) and (5) treatment.

Included in the last item is eliciting the patient's therapeutic goals and criteria for evaluating treatment as successful or not. These questions must be asked in a permissive atmosphere without the clinician swaying the patient's views with his or her own ideas, and without expressing criticism of these views—which might prevent the patient from saying what is meant or feared. After eliciting the patient's explanatory model the clinician next assesses the meaning of sickness for that patient. At this point, the surgeon can follow Lipowski's[19] approach, which states that the experience of illness usually has only one of four potential meanings for patients: threat, loss, gain or no significance.

The patient in our case report gave the following explanation of her condition. She had few medical problems before the operation, felt normal psychologically, and had a satisfying life as far as job, interpersonal relationships, financial matters, and her family were concerned. After the operation she felt she had lost a part of her body and had suffered side effects that made her life unbearable. She grew profoundly depressed and had substantial problems in every sphere of her life. She attributed all of these symptoms and difficulties to the operation, including the life problems, and wanted to have the surgeons reanastomose her bowel immediately in order to resolve this unacceptable situation. Her perception was that the physicians understood neither the severity of her problems nor her desperation. She, clearly, saw the resulting illness and other side effects as a severe loss in Lipowski's terms. The patient wanted another operation as soon as possible in order to return to her former way of life.

Step 2

From the patient's own explanation and assessment of the meaning of the illness experience, the surgeon can develop a list of the "illness problems," such as the experiential, interpersonal, family, economic, occupational and cultural problems created by the disease. For example, a myocardial infarction in an active executive might cause loss of his job and means of income, sexual problems due to fear of precipitating chest pain, marital problems and depression. These can be listed in the chart alongside the "disease problems," such as diagnosis, evaluation of clinical status and possible complications. By assessing illness problems, a surgeon can then take a comprehensive approach to the best treatment for the patient and decide upon appropriate psychosocial interventions or referral (to colleagues such as a social worker, psychologist, psychiatrist or vocational rehabilitation counselor). We have listed in Table 1 several of the most frequent illness problems.

Our patient's illness problems include the following: (1) financial troubles owing to recurrent hospital admissions, (2) vocational problems created by absences due to her illness and recuperation from the operation, (3) interpersonal difficulties with her boyfriend, (4) depression with concomitant symptoms of insomnia, increased negative feelings in the morning, decreased energy

and, eventually, suicidal behavior, (5) social withdrawal resulting from her embarrassment over flatulence and fecal incontinence, and (6) unacceptable change in body image.

The clinical interventions that resulted included, first, psychiatric consultation and treatment with tricyclic antidepressants and psychotherapy. Psychotherapy focused on her problems of body image, including the subsequent experience of psychological loss and depression. A second result was an attempt to find a support group of other people who had undergone intestinal bypass operations. A third was social service consultation to help with vocational and financial problems.

Step 3

The surgeon should then compare his explanatory model with the patient's model and analyze the discrepancies between the two and their potential impact on care. Then, most important, the surgeon may choose to bring the areas of conflict out in the open in order to negotiate possible compromises with the patient so that the disagreement can be resolved. Evidence suggests that structuring the clinical process as a negotiation, rather than as an authoritarian relationship has beneficial effects on patient compliance, satisfaction and management problems.[11-16] The actual process by which surgeon-patient negotiations may be established is characterized by the following seven steps:

1. Elicit the patient's explanation of his or her illness and determine the major illness problems.
2. Facilitate the patient's decision regarding the type of treatment he or she desires.
3. Then, based on recognition of the patient's illness problems and his own biomedical knowledge of the physiological problems, the surgeon should clearly and fully present his explanatory model of the disorder and his treatment recommendations to the patient.
4. Where there are discrepancies between the patient's expectation of treatment and the doctor's recommendation, the surgeon should openly acknowledge and clarify the conflicts between the differing treatment objectives. He may wish to provide data and references to argue on behalf of his perspective and the treatment interventions it entails.
5. At times, an understanding of one another's conflicting explanations will lead to a change in one of the positions. In this case, a mutually acceptable plan for treatment can be agreed upon.
6. Where conflict cannot be resolved through such an understanding, the physician should decide on an acceptable compromise in treatment, based on his medical knowledge, recognition of the patient's explanatory model and illness problems, and his own ethical standards. The physician may decide to get opinions from the family, other health professionals (including social workers, ethnic and pastoral counselors or psychiatrists), or other agencies to help implement a compromise.
7. Throughout this process, it is essential for the surgeon to recognize that his role is to provide expert advice and rationale for specific treatment recommendations, but that the patient is the final arbiter of whatever choice is made. If a stalemate in negotiation is reached and the patient's decision remains unacceptable on biomedical or ethical grounds to the doctor, then the therapeutic contract is abridged. At this point the patient should be offered a referral to another physician.

In comparing the patient's explanatory model of her illness with her previous doctors' models it was apparent that there were significant discrepancies. As stated earlier, the patient viewed her surgical outcome as catastrophic, with serious illness problems in all significant psychosocial areas. However, her physicians felt that the surgical outcome was positive because of the 100 pound loss of weight and the return of her blood pressure to normal levels. The side effects, moreover, were felt to be a predictable result of the malabsorption syndrome created by the bypass, itself an expected physiological effect. The patient was told that these could be adequately controlled without another surgical intervention. At the time we first interviewed the patient she was severely depressed and was very angry with her surgeons, whom she viewed as taking an unempathetic stand that was unresponsive to her needs. She demanded that they reanastomose her bowel or she would consider suicide.

Our own explanatory model of this patient's problem indicated that she had several positive consequences of the operation, including losing 100 pounds and becoming normotensive, but that she had also suffered serious illness problems as a direct result of the bypass, thereby experiencing a devastating change in her former life-style. We recommended a treatment plan instituting care for both the medical management of her physiological side effects as well as psychosocial interventions, such as social work assistance with fi-

nancial and vocational difficulties, psychotherapy focusing on her depression and problems of body image and a course of tricyclic antidepressants. The patient did not agree to this plan, stating that she wanted another operation immediately. We then offered a clear statement that focused on the fact that there was patient-doctor disagreement about the type of treatment desired (the patient wanted immediate surgical intervention, whereas her surgeons and consultants felt conservative medical and psychosocial management were optimum). We, in concert with the surgeons, presented a compromise plan to manage the patient's care for three months on the lines outlined above. If the patient agreed to go along with this part of the plan, then we would agree that at the end of three months, if the patient continued to experience severe medical and illness problems, the surgeons would reoperate to reanastomose her bowel. The patient agreed to this compromise plan.

Our patient continued to have diarrhea refractory to all medications after discharge with 10 to 20 bowel movements per day. As a result, approximately two months after the initial evaluation the surgical team agreed to reanastomose her jejunoileal bypass. In addition, the patient was offered an alternative procedure, a reduction gastroplasty, in order to continue to maintain her weight and blood pressure. The patient agreed to this operation, which was carried out at the time of the reanastomosis. The patient has done well since then, with maintenance of her weight loss and no further problems with diarrhea.

Her psychosocial problems have been substantially alleviated as well. Her depression cleared, she married her boyfriend and has become active socially once again. Her relationship with the surgical team greatly improved and she has been followed in their clinic on a regular basis with high compliance and satisfaction.

Conclusion

We have presented a case report to show the importance of assessing illness problems, the patient's explanatory model of illness and a *negotiation model* in both preoperative and postoperative evaluation of surgical outcome. These interventions are vital in providing comprehensive health care that includes consideration of psychosocial as well as biomedical problems.

The case discussed is an example of the potentially disastrous consequences (in this situation, a near suicide) that can result when this integrated biopsychosocial approach is not taken. In addition, we have described a step-by-step method that can be incorporated into the evaluation and care of patients. We feel this method may help improve clinical communication and thereby decrease patient noncompliance, aid in understanding doctor-patient conflicts, decrease patient dissatisfaction and, perhaps, ultimately decrease medical-legal suits. Primarily, however, it is a mode of intervention that is intended to provide a systematic approach to comprehensive biopsychosocial surgical care of patients that can be directly applied by physicians themselves in routine surgical practice.

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Isolated Aortocoronary Bypass Operations in Patients Over 70 Years of Age

A Comparison With Results in Patients 50 to 59 Years Old

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The early and late morbidity, mortality and beneficial effects of isolated aortocoronary bypass operations in a group of 35 patients 70 years old or older were compared with those factors in patients 50 to 59 years old. The patients in both groups were matched according to the year in which the operation was done and the number of vessels bypassed. Left ventricular function, estimated by the angiographically calculated ejection fraction, was not statistically different in the two groups. Cardiac index, while adequate in both groups, was significantly lower in the older age group. Comparisons were made of "early" events, such as perioperative myocardial infarction, perioperative death and length of postoperative hospital stay; and of "late" events, including myocardial infarction, angina pectoris, congestive heart failure and death, which occurred after patients were discharged from the hospital. The mean length of follow-up of patients was similar in both groups.

In comparing early events in the two groups, there was no statistically significant difference in the incidence of perioperative myocardial infarction, perioperative mortality or mean length of postoperative hospital stays. With regard to late events, there was no statistically significant difference in the incidences of myocardial infarction, angina pectoris or mortality.

THE INDICATIONS FOR isolated aortocoronary bypass (IACB) operations continue to evolve. The initial indication was to alleviate angina pectoris unresponsive to medical therapy in young and middle-aged patients.[1,2] Subsequently, suitable candidates for this procedure have included those with unstable angina pectoris[3,4] and those with angina pectoris following acute myocardial infarction.[5] More recently, controversy has arisen as some surgeons have begun to carry out IACB operations in asymptomatic patients in whom treadmill exercise testing and radioactive isotope myocardial perfusion scanning have detected myocardial ischemia, and in whom subsequent coronary arteriography has shown significant coronary artery stenoses.[6] Controversy also surrounds the suitability of IACB operations in the *elderly,* a term generally used to refer to patients 70 years or older. As this growing segment of the population seeks medical assistance for the relief of angina pectoris, questions have been raised concerning morbidity, mortality, long-term results and,

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ABBREVIATIONS USED IN TEXT
CK = creatine kinase
IACB = isolated aortocoronary bypass
LDH = lactate dehydrogenase

TABLE 1.—*Number of Patients 70 Years Old and Older Having IACB Operations in Specific Calendar Years*

	1973	1974	1975	1976	1977	1978	Total
Number of patients . .	1	2	5	4	7	16	35

IACB = isolated aortocoronary bypass

therefore, the cost-effectiveness of this procedure. In an attempt to answer these questions we have reviewed the results of IACB operations in 35 patients, aged 70 years or older, who were operated on consecutively, and compared them with those of patients 50 to 59 years old. Patients in both groups were also matched for the number of vessels bypassed.

Patients and Methods

The records of all patients having IACB operations at Pacific Medical Center, San Francisco, by one surgeon were reviewed. This operation was first done at this institution in 1968. During the study period, January 1973 through December 1978, this surgeon carried out 472 IACB operations.

The study group consisted of 35 patients (consecutively operated on) 70 years of age and older (mean age 74.5 years, range 70 to 82), the first study patient having been operated on in March 1973. The number of elderly patients operated on for each calendar year is shown in Table 1. To compare the effects of age alone on the results of IACB, a control group of patients 50 to 59 years old (mean age 54.6 years) was selected. The control patients were chosen by obtaining for each calendar year a list of all patients 50 to 59 years old who had IACB operations. These patients were then matched with the elderly patients with respect to the year in which the operation was done and the number and location of diseased coronary arteries bypassed. Although the left ventricular ejection fraction was not specifically matched in the patients, there was no statistically significant difference in this measurement between the two groups (0.63 ± 0.1 versus 0.59 ± 0.1, $P = 0.2$). Neither were cardiac indices specifically matched between the two groups, and the cardiac index in the older age group was significantly lower than in the younger age group (2.3 ± 0.5 versus 2.6 ± 0.6, $P = 0.04$). The similarities in the ejection fractions and cardiac indices in patients in both groups reflect the fact that selection of patients for IACB required them to have adequate left ventricular function and adequate hemodynamics.

Because there were many more patients in the 50-to-59-year age group than in the 70-year-and-older age group, control patients were randomly chosen from the total number operated on. However, to insure that the control group was representative of all patients in the younger age group, twice as many controls as elderly patients were selected.

All patients had preoperative cardiac catheterization and angiographic studies, which included measurement of left ventricular end-diastolic pressure, determination of cardiac output (index) by the dye dilution or direct Fick methods, and left cineventriculography in both right anterior oblique (RAO) and left anterior oblique projections. The left ventricular ejection fraction was calculated by the area-length method or the length-minor diameter method after tracing end-diastolic and end-systolic contours from the RAO projection of the left cineventriculogram. Selective coronary arteriography was done using the Judkins technique in most patients, and the Sones technique in a few.

Preoperative symptoms in all patients were assessed by review of hospital and office records. In 1978 and 1979 attempts were made to contact all patients or their physicians to evaluate the late results of the procedure. Only one patient (aged 59 years) was lost to follow-up. The duration of follow-up ranged from three months to five years in both older and younger groups (mean 17.7 ± 13.4 versus 16.7 ± 13.6 months, $P = 0.7$). As the management of patients undergoing an IACB operation has been progressively improved by preoperative administration of beta-blocking medications[7] and vasodilators,[8,9] by the perioperative use of intra-aortic balloon counter-pulsation,[10] by the intraoperative use of cold cardioplegic solution for myocardial preservation,[11] and by postoperative encouragement of earlier ambulation, the results of the operation in the study group and control group were matched in each calendar year. Specific measurements evaluated were (1) incidence of perioperative myocardial infarction, (2) incidence of perioperative death, (3) duration of hospital stay from time of operation to the time of discharge, (4) incidence of late postoperative myocardial infarction, (5) incidence of postoperative angina pectoris, (6) incidence of postoperative congestive heart failure and (7) incidence

of death following discharge. Statistical analysis was carried out using the two-sample *t* test.[12] Because electrocardiographic changes, and elevations in serum creatine kinase (CK) and lactate dehydrogenase (LDH) are difficult to interpret in the perioperative period, the diagnosis of perioperative myocardial infarction was made *only* if (1) new pathological Q waves appeared in the electrocardiogram (ECG), (2) if the concentration of the MB fraction of CK exceeded 30 IU per ml. or (3) if the serum level of LDH exceeded 300 IU per ml and the LDH_1 exceeded LDH_2. After hospital discharge the diagnosis of myocardial infarction was made by the patient's physician on the basis of the development of pathological Q waves and the generally accepted rises of CK and LDH isoenzymes. The postoperative return of angina pectoris was said to occur if the patient's physician felt, on the basis of the history taken, that the patient indeed had a return of symptoms suggesting myocardial ischemia, recognizing the difficulties in establishing myocardial ischemia as a cause of chest discomfort.[13]

Results

Early Results

Perioperative myocardial infarction was detected in 8.6 percent (3 of 35) of the older patients, and in 21 percent (15 of 70) of the younger patients (P = 0.2). In only one patient in the older age group and in only two patients in the younger age group could the diagnosis of myocardial infarction be established by ECG criteria.

There was one perioperative cause of death in each group, both deaths felt to be the result of myocardial infarction suffered during the procedure. The older patient died 14 days after the operation and the younger patient died in the operating room. The perioperative mortality was 2.9 percent (1 of 35) in the older, and 1.4 percent (1 of 70) in the younger age group (P = 1.0) (see Table 2).

The length of hospital stay was slightly longer for the older age group (mean 14.0 days, range 10 to 32) than for the younger age group (mean 12.3 days, range 9 to 60) (P = 0.2).

Late Postoperative Events

In the follow-up period, 11 percent (4 of 35) of the elderly patients, and 8.6 percent (6 of 70) of the younger patients suffered acute myocardial infarction, but the difference between the two groups was not statistically significant (P = 0.9).

Angina pectoris recurred in 34 percent (12 of 35) of the older patients and in 36 percent (25 of 70) of the younger patients (P = 1.0). Late death occurred in 8.6 percent (3 of 35) of the elderly patients, and in only 1.4 percent (1 of 70) of the younger patients, but this difference was not statistically significant (P = 0.2), probably because of the small number of patients in the study who died. Of the older patients, one died of congestive heart failure in the course of an acute myocardial infarction two months after the operation; another died of an acute arrhythmia a year postoperatively, and the third died suddenly, but without a perimortem diagnosis. The only death in the younger age group occurred at the time of an acute myocardial infarction three years after the operation.

Discussion

Over the past decade it has become clear that cardiac operations for valvular heart disease can produce excellent clinical results and can be carried out in the elderly with a death rate that is only slightly higher than in younger patients.[14,15] Less clear are the results and operative mortality of isolated aortocoronary bypass operations in older patients *compared with younger ones.*[16-18] Many studies have shown that prognosis in symptomatic patients with coronary artery disease who have *not* been operated on is related to the number of significantly narrowed vessels,[19-21] and to

TABLE 2.—*Comparison of Preoperative Hemodynamic Data, Perioperative Events and Postdischarge Events in the Two Age Groups*

	Preoperative Hemodynamic Data		*Perioperative Events*			*Postdischarge Events*			
Age of Patients (Yrs)	*Left Ventricular Ejection Fraction*	*Cardiac Index (L/Min/M²)*	*MI*	*Death*	*Hospital Stay (Days)*	*MI*	*Angina Pectoris*	*Congestive Heart Failure*	*Death*
≥70 (N=35)	0.63±0.1	2.3±0.5	8.6%	2.9%	14.0	11.0%	34.0%	8.6%	8.6%
50-59 (N=70)	0.59±0.1	2.6±0.6	21.0%	1.4%	12.3	8.6%	36.0%	5.7%	1.4%
P value	0.2	0.04	0.2	1.0	0.2	0.9	1.0	0.9	0.2

MI = myocardial infarction

the state of left ventricular function best assessed by the angiographically calculated left ventricular ejection fraction.[22,23] The clinical results of an IACB procedure in symptomatic patients with coronary artery disease also appear to be related to the number of significantly narrowed vessels and to the left ventricular ejection fraction.[24,25] However, operative success is also dependent on technical considerations such as the size and contour of the vessels beyond the site of anastomosis and the viability of myocardium fed by the bypassed vessels.[26]

The effects of old age alone on the results of an IACB operation have not, to our knowledge, been carefully examined. In this study we compared the clinical results of an IACB in patients (consecutively operated on) over 70 years old with those in patients 50 to 59 years old, both groups being matched for the number of vessels bypassed. We chose the specific age group of 50 to 59 years as a control group because these patients make up the largest number having IACB operations in our institution. The use of this specific age group also avoids comparison with patients who are so close in age to patients in the study group that age alone might not be a distinguishing factor, and avoids comparison with those who are so much younger than the elderly patients that age alone (in relation to such factors as employment or physical activities) might affect the results. We looked at early events to see if this operation is tolerated differently by patients in the two age groups, and at late events to see if the effects of the operation were comparable in the two groups. There were no statistically significant differences in the incidences of perioperative myocardial infarction, death or length of postoperative hospital stay between the two groups, indicating that elderly patients can tolerate IACB operations as well as those in the younger group.

Similarly, there were no statistically significant differences in the incidences of late myocardial infarction, angina pectoris, congestive heart failure or death. The 34 percent recurrence rate of angina pectoris in both groups was slightly higher than that reported in the literature from other major centers.[27,28] The time to recurrence of angina pectoris in our patients ranged from 1 to 24 months (mean 8 months) after the operation. The higher mortality in the older age group, compared with that in the younger one (3 of 35 versus 1 of 70 patients), is not a statistically significant difference. However, the failure to achieve statistical significance may be related to the small number of patients who died in each group.

Conclusion

On the basis of these data, we conclude that in patients over the age of 70 years who have good ventricular function, IACB operations can be done with early and late postoperative results similar to those in younger patients, 50 to 59 years old.

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Diagnosing Pancreatic Cancer

An Analysis of Several Strategies

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The usefulness of a clinical examination was compared with several other procedures (ultrasonography, pancreatic function tests, endoscopic retrograde cholangiopancreatography and angiography) for diagnosing pancreatic cancer. We used a simplified form of decision analysis to show the effects of different strategies on direct diagnostic costs, missed diagnoses and false-positive diagnoses.

Our analysis indicates that existing laboratory tests are either too nonspecific or too invasive to be used successfully as screening tests for pancreatic cancer. To decrease the number of unnecessary laparotomies due to false-positive test findings, patients should have a high probability of pancreatic cancer, based on clinical criteria, before further testing is carried out. In fact, exisiting clinical criteria are both sensitive and specific for pancreatic cancer.

PANCREATIC CANCER, because of its relatively high incidence and mortality, continues to frustrate physicians. There is no successful therapy for advanced disease, and early diagnosis seems to be the only feasible possibility for improving chances for survival. Rapid improvement in diagnostic techniques for evaluation of the pancreas has added further impetus to this possibility. Physicians hoping to diagnose pancreatic cancer that can be treated will probably make greater use of these diagnostic tests.

Clinicians who wish to evaluate patients for the possibility of pancreatic cancer can choose from a large number of tests. Included among these are pancreatic function tests (PFT), ultrasonography (US), radionuclide scanning of the pancreas, duodenal cytologic studies, endoscopic retrograde cholangiopancreatography (ERCP), pancreatic angiography (ANGIO) and computerized tomography (CT). Published studies have provided a great deal of information about the accuracy of each of these procedures, and it is clear that none of them is perfect. Although a few authors[1,2] have suggested strategies for diagnosing pancreatic cancer, the choice of the most appropriate approach is not easy.

The following analysis attempts to provide a practical framework from which to choose a diagnostic strategy for pancreatic cancer. Using the techniques of decision analysis and published data about test performance, we have tried to esti-

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ABBREVIATIONS USED IN TEXT

ANGIO = angiography (of the pancreatic vessels)
CRIT = clinical criteria used to diagnose pancreatic cancer
ERCP = endoscopic retrograde cholangiopancreatography
PFT = pancreatic function tests
US = ultrasonography (abdominal)

TABLE 1.—*Performance Characteristics of Tests for Pancreatic Cancer**

Test	*Sensitivity*	*Specificity*
ERCP	0.95	0.90
Angiography	0.70	0.95
Ultrasound†	0.75	0.85
Pancreatic function test†	0.90	0.80

ERCP = endoscopic retrograde cholangiopancreatography

*From DiMagno et al.[5, p737]

†The sensitivity and specificity refers to the ability of these tests to detect any kind of pancreatic disease.

mate the values of several diagnostic approaches. This analysis illustrates the pitfalls encountered in screening for disease and the compromises one must make to maximize the diagnosis of disease.

The analysis also suggests that a relatively simple clinical evaluation may assist in making the diagnosis of pancreatic cancer and should be an important part of any diagnostic strategy.

Methods

Our approach to comparing diagnostic strategies involves the use of decision analysis. Simply put, decision analysis is a quantitative approach to problem solving that allows one to estimate and compare the values of different strategies or decisions in the face of uncertainty.[3,4]

To use this analytic tool to compare strategies for diagnosing pancreatic cancer, certain kinds of data are required. They include the following: (1) The specificity of each test. This measure of the degree to which a test will be falsely positive is defined as the proportion of people without disease in whom there is a positive test result. (2) The cost of a false-positive result. This refers to the cost (not always measured in dollars) of errors made as the result of a positive test in nondiseased patients (such as the consequences of unnecessary therapy or further testing, or the erroneous labeling of a patient as having the disease). (3) The sensitivity of a test. This measure of the degree to which a test detects disease is defined as the proportion of all patients with disease who have an abnormal test result. (4) The cost of a false-negative test result. This is the cost incurred as the result of a missed or delayed diagnosis. (5) The prevalence of the disease in the population to which the test is to be applied. (6) The predictive value of a test. This measure of test accuracy is defined as either the percent of positive results that are true positives (positive predictive value) or the percent of negative results that are true negatives (negative predictive value). It may be calculated if test sensitivity, test specificity and disease prevalence are known. (7) The risks and direct costs of the test to be used. Although decision analysis often tries to convert all costs and benefits into a single unit of measurement (generally monetary), this is usually unrealistic for medical problems. Our analysis will avoid this problem by using monetary costs only where they are directly measurable. Other costs and benefits will not be quantified, as they often depend on the values of the individual patient or physician.

Given the above definitions and considerations, we shall compare strategies that use combinations of the following tests: ERCP, US*, ANGIO, PFT and specific aspects of the history and physical examination or clinical criteria (CRIT). We shall estimate the sensitivity and specificity of this last *test* using available data and certain assumptions, which will be discussed below. The sensitivity and specificity (Table 1) of the other diagnostic tests have been obtained primarily from the studies of DiMagno and associates.[5] Other published data agree fairly well with their findings,[6-10] but theirs is the only study in which PFT, US, ERCP and ANGIO were all evaluated prospectively for the same patients. Using clinical criteria (discussed in the next section), they selected 70 people to undergo each of the following tests: US, ERCP, ANGIO and PFT. In each patient either a laparotomy or liver biopsy was carried out to determine the diagnosis of pancreatic cancer; the disease was present in 30 of the patients (a prevalence of 43 percent). The sensitivity and specificity of each diagnostic test was then calculated from the prevalence of positive test results in diseased (pancreatic cancer) and nondiseased (no pancreatic cancer) patients, respectively.

Finally, a complete decision model of the

*Although we will not specifically deal with computerized tomography, present data suggest that the performance of this test is very similar to that of ultrasonography.

evaluation of patients suspected of having pancreatic cancer requires knowing the sensitivity, specificity and predictive value of the clinical evaluation that usually precedes the decision to carry out US, PFT, ERCP or ANGIO. DiMagno's study[5] is unique because it provides a basis for calculating these criteria for the initial clinical evaluation. They selected patients for more extensive studies if they had had at least two of the following five findings for 18 months or less: (1) Upper abdominal pain; (2) abdominal pain with nocturnal awakening or radiation of pain into the back; (3) weight loss of 10 percent of ideal body weight; (4) unexplained obstructive jaundice, and (5) unexplained pancreatitis. An additional requirement was that physical examination, routine laboratory tests (except as associated with jaundice) and results of conventional gastrointestinal x-ray films be normal.

DiMagno's study provides us with the *predictive value* of their clinical criteria: 43 percent of the patients who satisfied their criteria actually had pancreatic cancer. The *sensitivity* of their criteria can be estimated from published data: It has been observed that 70 percent to 80 percent of patients with pancreatic cancer have abdominal pain, weight loss, or jaundice,[11-14] and many patients have at least two of these attributes. Therefore, we have assumed that 75 percent of patients with pancreatic cancer would satisfy the criteria used by DiMagno and associates (a sensitivity of 0.75).

The *specificity* of these criteria is not available in any published form, but can be calculated using Bayes's formula.[15] Bayes's formula states:

$$p(CA|CRIT+) = \frac{p(CA) \times p(CRIT+|CA)}{p(CA) \times p(CRIT+|CA) + [1 - p(CA)] \times p(CRIT+|\text{not } CA)}$$

The terms of Bayes' formula are defined as follows:

- $p(CA|CRIT+)$ is the probability of having pancreatic cancer, given a positive response to the clinical criteria (posterior probability), and is the same as the predictive value. In this case, $p(CA|CRIT+)$ equals 0.43, based on DiMagno's data.
- $p(CA)$ is the prevalence of pancreatic cancer in the population to whom initial screening criteria for pancreatic cancer are applied (earlier probability). The prevalence of pancreatic cancer has been found to be about 4 cases per 1,000 unselected patients with abdominal pain[12] and about 30 cases of cancer per 1,000 patients with jaundice.[11] The prevalence of pancreatic cancer among all patients in hospital has been reported to be 0.9 cases per 1,000 patients.[13] We selected the intermediate figure of 10 per 1,000 as a reasonable estimate of the prevalence of pancreatic cancer in the population initially screened for inclusion in the DiMagno study.

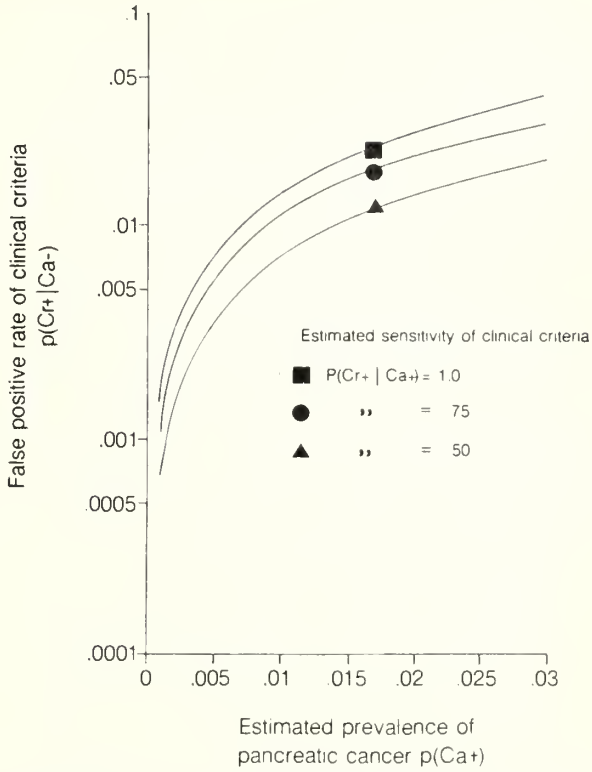

Figure 1.—Estimate of false-positive results of clinical criteria for diagnosing pancreatic cancer, based on variations in sensitivity and disease frequency. This figure shows that wide variations in prevalence of pancreatic cancer and sensitivity of the clinical criteria have only a modest effect on the rate of of false-positive results of these criteria.

- $p(CRIT+|CA)$ is the probability of having at least two of the screening criteria, given the presence of pancreatic cancer (true positive rate). We have used published data to set this figure at 0.75.[11,13-15]
- $p(CRIT+|\text{not } CA)$ is the false-positive rate of the criteria, which we wish to estimate using Bayes' formula.

$$0.43 = \frac{(0.01)\ (0.75)}{(0.01)\ (0.75) \times (0.99)\ p\ (CRIT+|\text{not } CA)}$$

$p(CRIT+|\text{not } CA)$ equals 0.01. Therefore, the specificity of the criteria is 0.99. This high specificity should not be surprising because any test or

maneuver which successfully selects a population with a relatively high frequency of an uncommon illness (as was the case with DiMagno's criteria) must have very few false-positive results. Figure 1 shows that wide variations in the assumed values for p(CA) and p(CRIT+|CA) have little effect on our estimate of the specificity of the clinical criteria.

Results

To compare one diagnostic approach with another, we will assess the cost and diagnostic accuracy of five different diagnostic strategies. These strategies represent a wide spectrum of possible approaches to diagnosing pancreatic cancer, ranging from a maximal to a minimal amount of testing:

- Strategy 1
  - Do US on everyone with abdominal pain.
  - If US findings are negative, do PFT.
  - Do ERCP or ANGIO on patients with either abnormal US or PFT results.
  - If ERCP or ANGIO shows possible cancer, do a laparotomy.
- Strategy 2
  - Do US on everyone.
  - If US gives abnormal results, do ERCP or ANGIO.
  - If ERCP (or ANGIO) shows possible cancer, do a laparotomy.
- Strategy 3
  - Apply the clinical criteria of DiMagno and colleagues.[5]
  - If a patient has at least two clinical criteria, proceed to strategy 1.
- Strategy 4
  - Apply the clinical criteria.
  - If the patient has two or more of the criteria, do ERCP.
  - If ERCP shows possible cancer, do a laparotomy.
- Strategy 5
  - Apply the clinical criteria.
  - If the patient has two or more of the criteria, proceed directly to a laparotomy.

Next, let us assume a population of 10,000 patients with chronic abdominal pain. We estimate the prevalence of pancreatic cancer in patients with abdominal pain to be 0.01; therefore, there will be 100 patients with pancreatic cancer. We then calculate how many people will have positive and negative test results and how many will eventually undergo a laparotomy after using each of these strategies (Table 2). For example, in strategy 1, ultrasonography would be carried out for everyone in our hypothetical population, and the results would indicate possible cancer in 75 of 100 patients with cancer (sensitivity equals 0.75) and in 1,485 of the 9,900 patients without

TABLE 2.—*Outcomes of Five Strategies for Detecting Pancreatic Cancer in a Hypothetical Population of 10,000 Patients With Abdominal Pain*

	*Outcome**							
Strategy	*No. of Clinical Evaluations Done*	*No. of Ultrasound Tests Done*	*No. of PFT's Done*	*No. of ERCP Tests Done*	*Total Lab Costs†*	*Correctly Diagnosed Cancers (per 100)*	*No. of Laparotomies With Negative Results‡*	*Cost of Surgical Operation§*
1. Do US; if −, do PFT; if either test is +; do ERCP or ANGIO; if +, operate	0	10,000	8,440	3,266	$1,888,500	93	317	$2,050,000
2. Do US, if +, do ERCP or ANGIO; if +, operate	0	10,000	0	1,560	$1,040,000	71	149	$1,100,000
3. Apply clinical criteria; if +, apply strategy 1	10,000	174	103	105	$1,542,710	69	4	$ 365,000
4. Apply clinical criteria; if +, do ERCP, if +, operate	10,000	0	0	174	$1,543,500	71	10	$ 405,000
5. Apply clinical criteria; if +, operate	10,000	0	0	0	$1,500,000	75	99	$ 870,000

ANGIO = angiography; ERCP = endoscopic retrograde cholangiopancreatography; PFT = pancreatic function test; US = ultrasonography

*Does not include potential morbidity or mortality due to testing or surgical operation.

†Assumes: ultrasound test = $65, PFT = $50, ERCP = $250, clinical criteria (initial x-ray studies and blood tests) = $150.

‡Negative laparotomy is defined as laparotomy done on a patient without pancreatic cancer. However, the DiMagno criteria detected conditions that potentially would be benefitted by a surgical operation in 27.5 percent of the patients without pancreatic cancer. Thus, 3 of 10 people in strategy 4 and 27 of 99 people in strategy 5 might benefit from an operation.

§Assumes: 10 days in hospital plus an operation = $5,000.

cancer (specificity equals 0.85). The pancreatic function test, carried out on patients with normal US results would give abnormal findings in 23 of the 25 patients with cancer who had negative US findings (specificity equals 0.80) and in 1,683 noncancer patients (specificity equals 0.80). These figures assume that the results of the two tests are independent of each other. Therefore, there would be 3,266 patients who, because of abnormal US or PFT results, would undergo ERCP; findings of this test would be positive in 93 of the 98 cancer patients identified by US and PFT (a sensitivity of 0.95) and falsely positive in 317 of the noncancer patients identified by US and PFT (a specificity of 0.90). Thus, 93 of 100 patients with cancer would be correctly referred for a laparotomy, but 317 of 9,900 patients without cancer would undergo an unnecessary laparotomy. If angiography were used in strategy 1 instead of ERCP, there would be slightly fewer false-positives and 24 fewer true positives.

In strategy 3, at least two clinical criteria will be present in 75 of 100 cancer patients (a sensitivity of 0.75) and in 99 of 9,900 patients without cancer (a specificity of 0.99). Therefore, 174 of the initial 10,000 people would be suspected of having cancer from the clinical criteria. If US and PFT are done on these patients, there will be 105 patients in whom there are abnormal findings. As a result of ERCP being done on these 105 patients, 73 patients would undergo laparotomy, with 69 of the 100 cancer cases being detected.

Strategies 2, 4 and 5 have intermediate results, correctly identifying more cancer patients, but resulting in more unnecessary laparotomies than in strategy 3. As indicated by Table 1, one must do a large number of laparotomies on people without pancreatic cancer to diagnose more than two thirds of the patients with carcinoma. The use of clinical criteria to choose candidates for further diagnostic tests results in the lowest costs and fewest unnecessary laparotomies; however, these economies are associated with a lower rate of correctly diagnosed cancer as well.

Discussion

Our model points out that attempts at maximizing the number of correct diagnoses in patients with cancer will subject some patients without disease to invasive or expensive tests. In particular, this analysis illustrates some of the effects of using tests with differing specificities and sensitivities on populations with variable disease prevalence. A major lesson of the analysis is that none of the existing tests for pancreatic cancer is perfect. Although some of the tests evaluated are considered noninvasive, we would consider them far from safe if a positive test result leads to carrying out a risky procedure (such as an ERCP[17] or a laparotomy). Because none of the tests or strategies yields a completely desirable outcome (that is, a correct diagnosis in all patients with cancer while avoiding surgical operations for all patients without cancer) it may be difficult to choose which approach to take.

In fact, several factors should influence a decision between competing strategies. These include (1) the nature of the disease in question (such as its reversibility, mortality and morbidity), (2) the diagnostic and therapeutic consequences of a positive test result and (3) the importance, to the physician and patient, of being certain of the diagnosis. Knowledge of test performance may affect how these factors are used in making a decision. For example, if an illness is relatively reversible by therapy, but carries a high mortality or morbidity if left untreated, then maximum detection of disease may be most important, and a sensitive, rather than specific, test is needed. On the other hand, if therapy is dangerous, expensive or only palliative, it may be desirable to strive for fewer false-positive results, even at the cost of failing to detect some disease in some patients. Again, one may wish to avoid using a test with a high false-positive rate if a positive result on that test will probably lead to doing a more dangerous test. For low-prevalence diseases, the cost of certainty may be high, because the probability of a rare condition may still be quite low even when results of a screening test are abnormal.

One aspect of the diagnostic process that is difficult to quantify is the "need to know." Both physician and patient may wish to minimize uncertainty, even if increased diagnostic certainty results in increased patient risk without leading to altered therapy or an improvement in the outcome. While it is usually impossible to measure the value of minimizing uncertainty, this factor may figure importantly in the decision to pursue a diagnostic evaluation. This model provides at least a partial estimate of the costs of increasing certainty. The patient and physician must decide if certainty is really worth the price.

Of course, if one is to use this model to aid in

the decision-making process, it is necessary to decide how valid the model actually is. First, it is likely that several of the tests analyzed are, if anything, less sensitive or specific than we have indicated. In another recent study of diagnostic tests for suspected pancreatic cancer, US, ANGIO and ERCP were found to have sensitivities and specificities that ranged between 0.68 and 0.83,[18] somewhat lower than found by DiMagno and associates.[5] The authors used clinical criteria to select patients for diagnostic studies that were very similar to those used in our model, and found pancreatic cancer in 64 percent of the 138 patients they operated on. This suggests that the clinical criteria may have an even greater predictive value than we indicated.

If it is true that the tests used for detecting pancreatic cancer are less sensitive and specific than we have indicated, while the clinical criteria are not, then the conclusions of our model would support even more strongly the use of clinical criteria as the first step in the diagnostic process. Nonetheless, the performance characteristics of the clinical criteria may be questioned, as they are based on assumptions about the prevalence of pancreatic cancer and the sensitivity of the clinical criteria. Because the prevalence of cancer is likely to vary from population to population it is important to estimate the effect of this variation on the predictions of the diagnostic model. Our analysis (known as a sensitivity analysis) shows that the rate of laparotomies giving positive results increases for all strategies as the probability of cancer increases (Figure 2). However, the percent of cancers diagnosed remains the same, and depends on the sensitivity of the tests. Regardless of the prevalence of pancreatic cancer, strategy 1 is always most likely to subject the most noncancer patients to a laparotomy, and strategy 3 is least likely to do so. On the other hand, strategy 1 also leads to a correct diagnosis in the highest proportion of cancer patients.

It is more difficult to look at the assumptions underlying the sensitivity of the clinical criteria. Clearly, the criteria we have used (abdominal pain, jaundice, weight loss, pancreatitis) are characteristic of cancer in its later stages and probably occur less often in early cancer than in late cancer. Thus, use of these conservative criteria is unlikely to help in the diagnosis of early, possibly treatable, cancer. Unfortunately, it has not been shown that any of the commonly used

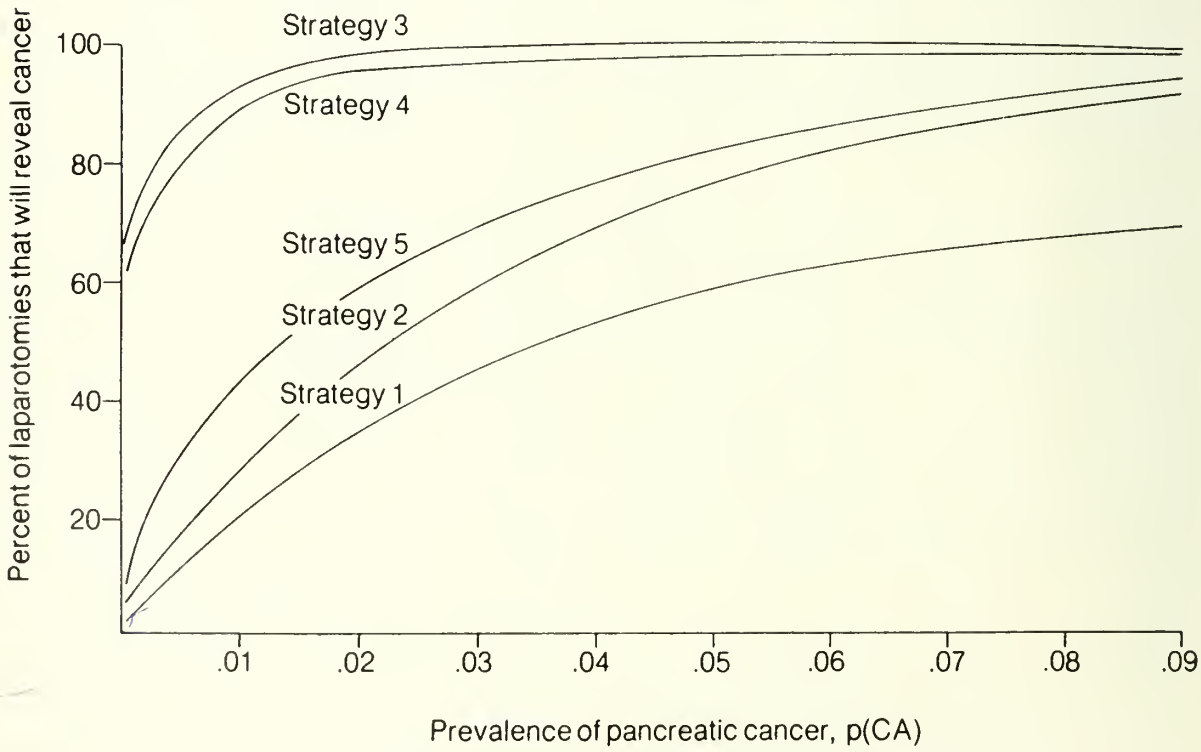

Figure 2.—The effect of the prevalence of pancreatic cancer on the number of laparotomies with abnormal findings. The figure illustrates that as the prevalence of cancer in the population under study increases, there will be fewer laparotomies not showing the presence of cancer.

tests for pancreatic cancer are capable of reliably detecting the disease in its early stages. Therefore, attempts at early diagnosis (that is, without using stringent clinical criteria for further investigations) are likely to yield, as our analysis indicates, a high proportion of false-positive diagnoses. Given the dismal results of present pancreatic cancer therapy, a vigorous search for disease is unlikely to be rewarding.

Conclusion

Our model is not designed to replace decision-makers. Rather, it can facilitate difficult choices by providing physicians and patients with a clear picture of the options available and an estimate of the outcomes associated with each option. Second, it can help guide further research by indicating areas for which data are lacking. For example, our analysis shows the need for further study of the comparative performance of the history, physical examination and laboratory tests, especially in light of several studies showing that a thorough clinical evaluation is often the most valuable determinant of the final diagnosis.[19-21] Finally, the model supports the idea that clinical decisions should carefully consider test sensitivity, specificity, costs and risks, as well as prevalence and ability to treat the disease.

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Thallium 201 Scintigraphy

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The radioactive isotope thallium 201 behaves physiologically as a potassium analog, and when injected intravenously accumulates rapidly within the cells of many organs. Uptake of the isotope reflects both regional perfusion and sodium-potassium pump activity. The radionuclide emits 80 keV x-rays which are suitable for scintillation camera imaging.

The main clinical application of ^{201}Tl scintigraphy has been in myocardial imaging. Abnormal uptake of the isotope results in a cold spot on the myocardial image. In patients with coronary artery disease, the differentiation of ischemic and infarcted myocardium is made by comparing images obtained after injecting the radionuclide at the peak of a maximal exercise test with those obtained after injection at rest. Abnormalities due to ischemia usually are seen only on the stress image whereas fixed defects in both rest and stress studies usually indicate areas of infarction or scarring. Some investigators believe that redistribution images obtained four to six hours after stress injection (without administering further ^{201}Tl) give the same information as a separate rest study. The sensitivity of stress imaging for detecting significant coronary disease is of the order of 80 percent to 95 percent, though computer processing of the images may be necessary to achieve the higher figure. The prediction of the extent of coronary disease from ^{201}Tl images is less reliable. An abnormal ^{201}Tl image is not entirely specific for coronary artery disease and the likelihood of an abnormal image being due to this diagnosis varies according to the clinical circumstances.

The main clinical value of ^{201}Tl myocardial imaging is likely to be in the noninvasive screening of patients with atypical chest pain or with ambiguous findings on stress electrocardiographic tests. It has also proved useful in studying patients with variant angina or following a coronary bypass operation. It is doubtful whether the technique is clinically helpful in most patients with suspected or established acute myocardial infarction.

Imaging of organs other than the heart with ^{201}Tl has received much less attention but has been reported in patients with peripheral vascular disease and various primary and secondary neoplasms.

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In 1941 Noonan and co-workers[1] showed that following intraperitoneal injection of potassium 42 into rats, there was rapid accumulation of radioactivity in the myocardium. In the early 1950's, work by Burch and associates[2-6] showed that radioactive rubidium could be regarded as an analog of potassium in tracer studies, though the behavior of the two elements was not identical. Similar properties were also described for radioactive cesium.[2]

The demonstration by Burch and colleagues of rapid myocardial uptake of rubidium 86 suggested to Carr and colleagues[7] the possibility of showing the myocardium by photoscanning after the administration of the radioactive isotope. They confirmed the feasibility of imaging the beating myocardium of dogs using ^{86}Rb and a rectilinear scanner, but found that areas of decreased isotope uptake due to experimental myocardial infarction could be identified reliably only after excision of the heart.[7] They considered ^{86}Rb unsuitable for in vivo imaging of the myocardium and turned their attention to cesium 131. Using this tracer, they reported the first successful imaging of normal myocardium in humans, and also showed that the images were abnormal in patients with acute myocardial infarction.[8]

Between 1964 and 1975 a variety of radioactive isotopes of potassium, rubidium and cesium were examined as possible myocardial imaging agents; however, for physical or biological reasons none was suitable for widespread use.[9] In 1976, however, the introduction of thallium 201 made myocardial imaging generally feasible,[10] and this has now become established as a clinically useful tool for investigation.

The heavy metal thallium was discovered and named in 1861 by the English chemist Sir William Crookes, the name being derived from the Greek word *thallos* (a budding twig), "a word which is frequently employed to express the beautiful green tint of vegetation and which I chose on account of the green line which it communicated to the spectrum, recalling with particular vividness the fresh colour of early spring."[11]

Physical and Biologcal Properties of Thallium

Thallium (atomic number 81) belongs to group III of the periodic table whereas potassium, rubidium and cesium are group I elements. However, in 1960 Mullins and Moore, noting that the univalent thallium cation had a crystal radius between that of potassium and cesium, felt that their physiological properties might be similar and showed that this was so in the isolated frog sartorius muscle preparation.[12] The biological similarities between potassium and thallium were confirmed by Gehring and Hammond in rabbit erythrocytes[13] and in studies in rats and dogs.[14] The first suggestion of thallium as a potassium analog for use in nuclear medicine was by Kawana and co-workers[15] in 1970. Using thallium 199, they showed the possibility of imaging the human myocardium; however, the images were of poor quality because of high energy gamma rays present, which caused excitation of the lead in the collimator. They suggested that thallium 201 might be more suitable. This was eventually produced from Brookhaven National Laboratory[10] and, in the form of a sterile solution of carrier-free thallous chloride in saline, is now the standard agent for noninvasive imaging of normal myocardium.

Thallium 201 has a physical half-life of 73.5 hours and decays by electron capture to mercury 201, emitting gamma rays of 137 and 167 keV. The ^{201}Hg then decays with emission of 65 to 82 keV x-rays. The gamma rays have suitable energies for scintillation camera imaging but are present in low incidence so that the use of the mercury x-rays is usually recommended. Atkins and colleagues[16] found that the count rate obtained using the x-rays was seven times greater than that with the gamma rays.

The mercury x-rays are not ideal for imaging. The relatively low energy leads to substantial tissue attenuation. In addition, the intrinsic resolution obtained with the scintillation camera using ^{201}Tl may be as much as 50 percent less than that with technetium 99m (6.7 mm versus 4.7 mm in one study[17(pp73-74)]).

Following intravenous injection, the uptake of ^{201}Tl occurs rapidly, with maximal myocardial uptake at rest occurring some 5 to 15 minutes after injection in different species.[16,18,19] The first pass extraction of the isotope from coronary arterial blood is of the order of 85 percent.[20,21] The myocardial-to-liver activity ratio obtained with thallium 201 is superior to that obtained with rubidium and cesium radionuclides,[22,23] and also to that with potassium 43.[19] Thallium is also superior to potassium radioactive isotopes in showing longer myocardial retention[19] so that multiple images are easier to obtain. Approximately 4

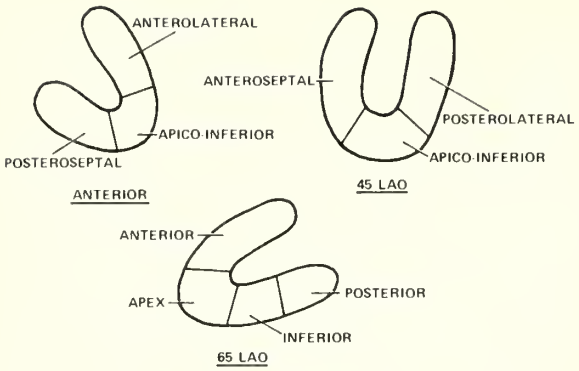

Figure 1.—Diagram of left ventricular regions seen in some standard projections for thallium 201 imaging. Note superimposition of apical and inferior myocardium on anterior and 45° left anterior oblique (LAO) projections.

percent of the injected dose of ^{201}Tl is taken up by myocardium.[10,24]

The myocardial uptake of ^{201}Tl, like that of the other potassium analogs, reflects two main factors —the regional myocardial blood flow and the metabolic integrity of the myocardial cells. In studies in animals there is good correspondence between decrease in coronary flow during experimental coronary occlusion and decrease of myocardial ^{201}Tl.[22] During coronary hyperemia, myocardial uptake of the isotope increases but to a lesser extent than myocardial blood flow.[22,24] The actual uptake of thallium by the myocardial cell is an active process which appears to use the adenosine triphosphatase-dependent sodium-potassium pump,[12-14] though there is some evidence to suggest that the mechanism of thallium uptake is not identical to that of potassium.[25] There is conflicting evidence at present as to whether reduced myocardial perfusion results in decreased myocardial ^{201}Tl uptake in the absence of myocardial ischemia, that is, disordered metabolism.[26-28]

Because myocardial uptake of potassium tracers is dependent on the integrity of each myocardial cell, metabolic effects may influence the trapping. Studies in animals have shown that hypoxia in the absence of any flow change will decrease the myocardial extraction rate of ^{201}Tl, and that metabolic acidosis has a similar effect.[20] Metabolic alkalosis, by comparison, augments myocardial ^{201}Tl uptake.[20,29]

The influence of some cardioactive drugs on ^{201}Tl uptake by the myocardium has also been studied. Two studies have reported depression of ^{201}Tl uptake after intravenous injection of propranolol or a cardiac glycoside,[24,30] though a third study failed to confirm this.[20] The administration of these drugs does not significantly degrade the quality of the in vivo myocardial image.[24] Insulin and glucose have been reported to cause substantial increase in myocardial uptake of potassium, rubidium and cesium,[3] but this effect has not been confirmed with thallium.[20] The myocardial uptake of ^{201}Tl is also increased following intravenous administration of dipyridamole, perhaps as a result of the coronary hyperemia that this drug induces.[24]

Methods

Myocardial imaging is carried out shortly after intravenous injection of thallous chloride Tl 201. The usual dosage used is limited to 1.5 to 2 mCi because of radiation dosimetry considerations (see below).

Images are obtained with a modern, standard field of view scintillation camera, though large field of view cameras can also be used. The spectrometer of the camera is centered over the 65 to 82 keV x-rays, usually with a 20 percent window. The collimation most frequently used is the general purpose, low-energy, high-resolution collimator, and this gives satisfactory images in most circumstances.[32] Acceptable images can also be obtained using a high-sensitivity collimator. Increased resolution can be obtained using a pinhole collimator but the low sensitivity precludes its general use.[32] Converging collimators have also been used, though there is some evidence that their ability to detect lesions is poor.[32] Recently, a multipinhole collimator system has been described which allows reconstruction tomography of the myocardium using ^{201}Tl.[33] This technique is still under investigation, but early results suggest a clinically significant improvement in the images.[34]

In most centers, images containing 250,000 to 500,000 counts are obtained, requiring some five to ten minutes for each image. Usually the images are "ungated," that is, they are recorded during all phases of the cardiac cycle and, thus, are blurred by cardiac motion. Gating the gamma camera by the patient's electrocardiogram (ECG) allows this blurring to be eliminated but prolongs the imaging time. There may, however, be important improvement in lesion detection with ECG gating.[35,36]

In a standard ^{201}Tl study, the principal contri-

bution to the left ventricular image is made by areas of myocardium that are perpendicular to or almost perpendicular to the front of the gamma camera.[37] Thus, by obtaining multiple projections, it is possible to view the different areas of the myocardium separately. These include an anterior view and one or more left anterior oblique views, as well as possibly a left lateral image. The images are usually obtained with the patient in a supine position, but two recent studies suggested that it is important to obtain the left lateral view with the patient lying on his right side. This is to avoid false posteroinferior defects being produced by attenuation of the low energy x-rays by the diaphragm.[38,39]

The precise anatomical areas of the left ventricle seen in any projection will vary somewhat depending on the orientation of the ventricle in the chest. Figure 1 shows one accepted system of nomenclature.

The two principal types of thallium 201 myocardial imaging studies are those carried out after injection of the tracer with the patient at rest and those after the tracer has been injected at the peak of a stress test.

Rest imaging should be done after the patient has been sitting quietly for a time. Rest images are characterized by a relatively poor ratio of myocardial-to-background activity with noticeable splanchnic, particularly hepatic, uptake. It is possible to reduce hepatic activity by injecting the patient in an upright position[10] and after some hours of fasting.[16,41]

Early studies with potassium analogs other than ^{201}Tl showed that acute myocardial infarction or myocardial scarring due to previous infarction could be shown by myocardial imaging after injection of the tracer at rest.[8,42-44] Such rest studies, however, usually showed no abnormalities in patients with coronary disease but no infarction. This is not surprising. As discussed above, regional myocardial perfusion is one of the two principal determinants of myocardial uptake of potassium analogs, and various studies using inert gas washout techniques have shown that regional myocardial perfusion may not be significantly changed at rest in patients with coronary disease and no infarction.[45,46] A very different circumstance exists during stress, however, as indicated by the elegant experiments carried out by the Seattle group. Both in animal and clinical studies they have shown that whereas myocardial perfusion distal to a coronary stenosis remains normal at rest until the lesion occupies 85 percent to 90 percent of the luminal diameter, during stress the normal augmentation in myocardial blood flow is decreased distal to stenoses of 50 percent or more.[47-49] The development of myocardial perfusion abnormalities during stress in patients with coronary artery disease, for whom results at rest were normal, has been confirmed using inert gas washout techniques.[50]

The radionuclide detection of relatively decreased perfusion distal to significant coronary artery occlusions during exercise predated the above investigations. In 1973 Strauss and coworkers[51] introduced the concept of stress myocardial imaging. They found that if ^{43}K was injected intravenously at the end point of a symptom-limited exercise test, abnormal myocardial images could be obtained in patients with coronary artery disease in whom rest myocardial images were normal.

The technique of stress imaging is now widely used. The patient exercises either on a bicycle ergometer or treadmill, under ECG control and with full resuscitation facilities available. When a standard exercise end point, such as chest pain, fatigue, maximal predicted heart rate or ST segment changes, is reached, the isotope is injected intravenously as a bolus and the patient is asked to continue exercising for at least 30 to 60 seconds more to allow fixing of the ^{201}Tl by the myocardium in its stressed state. Imaging then proceeds in the standard fashion. If imaging of the patient is done on two occasions after injection at the same exercise end point, the results are highly reproducible.[52]

Two pharmacological interventions have recently been described as alternatives to exercise stress testing. The intravenous injection of dipyridamole produces coronary vasodilatation and increased coronary artery blood flow[53] with increased myocardial uptake of ^{201}Tl in experimental animals.[24] Pharmacological dilatation of the coronary arterial tree using dipyridamole may be a satisfactory alternative to exercise stress testing for ^{201}Tl myocardial imaging in humans.[54,55] Imaging during an intravenous infusion of isoproterenol hydrochloride (Isuprel) has also been suggested as an alternative to exercise imaging.[56]

In 1977 Pohost and colleagues described the technique of redistribution imaging.[57] If the isotope is injected during stress, the images obtained

in the next 30 to 45 minutes reflect the distribution of uptake during stress. Over the next four to six hours, however, the thallium redistributes within the myocardium so that a delayed image obtained at that time, without further injection of tracer, is more a reflection of functional myocardial cell mass than myocardial perfusion.[58] Thus, it has been suggested that an ischemic area of myocardium will be abnormal on the images immediately following exercise but normal on the delayed images, whereas areas of infarction will be abnormal on both sets of images.[57,59] The value of delayed images following exercise in replacing separate rest studies will be discussed further in the section on coronary artery disease.

Interpreting Thallium 201 Myocardial Images

A variety of methods exist for interpreting ^{201}Tl myocardial images. Initial studies used unprocessed images recorded from the camera oscilloscope onto Polaroid or x-ray film, and in many centers this method is still used. Another approach has been to use computer-generated images, either in black and white or in color, and apply uniform background subtraction or contrast enhancement to them. Some observers have claimed that use of such processing improves the accuracy of interpretation of ^{201}Tl images,[60] but others believe it merely increases sensitivity at the expense of specificity.[61,62] A refinement of background subtraction is "interpolative background subtraction," which makes allowance for the differing background contribution in different tissues surrounding the myocardial image.[63]

Various methods of quantitative analysis of myocardial images have also been described recently. Attempts have been made to compare myocardial uptake of the radionuclide with activity in other organs.[64,65] However, such methods have been frustrated by the many factors which may alter such ratios. For example, hepatic activity is increased by a recent meal[16,41] or by injecting the patient when supine,[40] while lung uptake is increased and prolonged in smokers[66] and is frequently increased in multiple-vessel coronary artery disease after exercise—perhaps due to impaired left ventricular function.[67]

The alternative approach to "quantitation" has been to measure relative activity in different areas of the myocardium, and a variety of techniques have been described.[61,68-71] Use of such computer processing has not yet been clearly shown to produce significant improvement in interpretation of myocardial images when compared with visual analysis, but there have been some promising preliminary reports.[61,69,72]

The Normal Thallium 201 Myocardial Image

The normal left ventricular myocardium is seen on the ^{201}Tl image as a horseshoe shape, or sometimes a doughnut, of relatively uniform activity, with a central colder area corresponding to the left ventricular cavity (Figure 2). Even in the normal myocardium, uptake is not entirely uniform,[18,40,70,73] with the nonhomogeneity being more pronounced in rest than in stress studies.[40,70] The apex frequently appears as an area of thinning on normal images,[40] and decreased uptake is usually seen at the base of the heart at the sites of valve insertion.[40] In addition to more homogeneous cardiac uptake, the stress study is characterized by a higher myocardial-to-background activity ratio when compared with rest images.[40]

Visualization of the right ventricle is unusual on the rest image,[40] and if seen, suggests right ventricular overload or hypertrophy.[74,75] However, the right ventricle is frequently visualized on normal stress images (Figure 2).[40]

Safety of Myocardial Imaging

Like most heavy metals, thallium is a toxic substance, and serious (sometimes fatal) side effects to the central nervous system and gastrointestinal tract resulted from its use as a depilatory agent in the treatment of ringworm of the scalp.[76] Thallium salts have been used for homicidal poisoning both in fiction[77] and in fact.[78] Therapy for thallium poisoning is essentially supportive, though excretion may be promoted by potassium salts.[79]

The minimum lethal dose of thallium in humans is thought to be 8 to 12 mg per kg of body weight,[80] though nonfatal side effects have been reported with doses as low as 0.1 mg per kg.[18] Thallium 201 supplied for myocardial imaging is virtually carrier-free and the dose administered during diagnostic studies using 2 mCi of the radionuclide has been calculated to be of the order of 0.07 to 0.15 ng per kg of body weight,[73] so that there is a very large margin of safety, even when repeat studies are done. As yet there have

been no reports of ill effects following administration of this radioactive pharmaceutical agent.

The whole body radiation dose from ^{201}Tl is in the range of 0.07 to 0.24 rads per mCi.[16,18,58,81,82] The kidney is the critical organ, receiving a radiation dose of 0.39 to 1.17 rads per mCi. The renal medulla accumulates considerably more ^{201}Tl than the cortex.[18,24] The radiation dose sustained by the kidney during myocardial imaging is unlikely to produce any renal damage as no significant long-term functional or anatomical changes were seen in dog kidneys irradiated with 400 rads.[83]

The final potential hazard involved in myocardial imaging is that of exercising patients with suspected cardiac disease. Exercise testing for ECG studies in this group of patients is surprisingly safe, with a mortality of 0.5 to 1 per 10,000 and a nonfatal serious complication rate of 3 to 9 per 10,000 tests reported from two questionnaire surveys of many centers.[84,85] The hazard of exercising for stress myocardial imaging should be similar, but it is essential that (1) patients be assessed before the study for any known contraindications to exercise testing,[85] (2) the test be conducted by personnel fully trained in exercise testing, with full monitoring of the patient (including ECG) during and after exercise, and (3) that full resus-

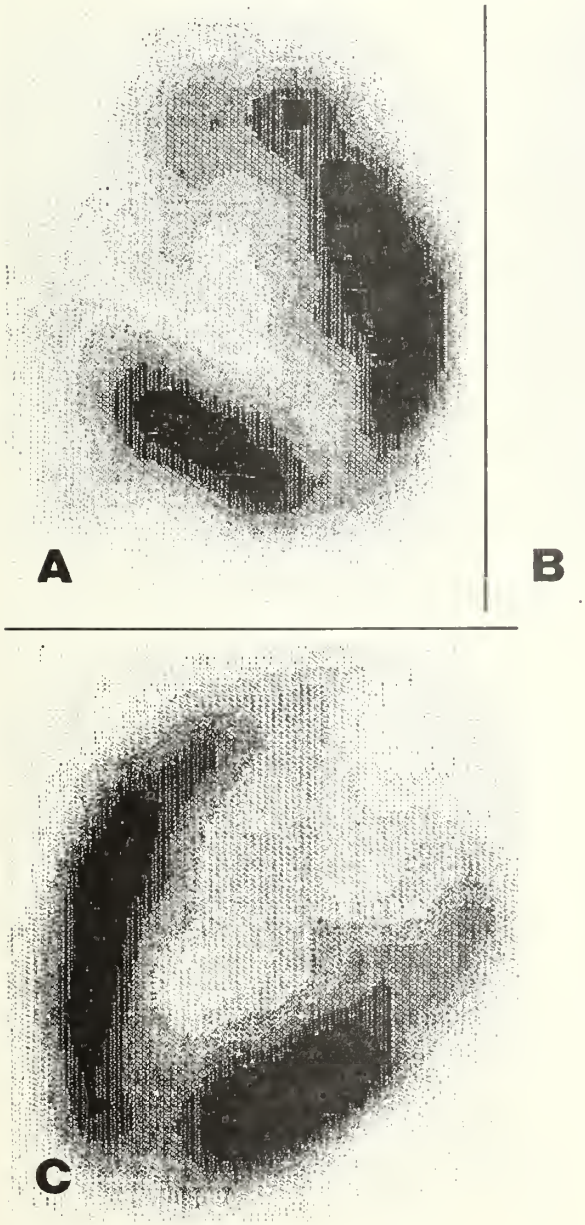

Figure 2.—Normal stress thallium 201 images **(A)** anterior, **(B)** 45° LAO and **(C)** 65° LAO. These images and those in Figures 3 to 6 have been processed using interpolative background subtraction (see Goris et al[63]). Note normal apical thinning on the anterior and 65° LAO images. Some right ventricular uptake can be seen on the 45° LAO image. Visualization of the right ventricle is normal on stress images but suggests right ventricular hypertophy if present on rest studies. There is a film artifact seen in the posterolateral region of the 45° LAO image; this is not of clinical significance. (LAO = left anterior oblique.)

citation facilities be available immediately if needed.

Clinical Applications of Thallium 201 Imaging

Ischemic Heart Disease

Acute myocardial infarction. The diagnosis of acute myocardial infarction often can be strongly suspected on clinical grounds. However, because of the large number of other conditions which may cause anterior chest pain and because of the serious implications that this diagnosis has for a patient's physical and psychosocial well-being both in the short and long term, the diagnosis should always be confirmed by appropriate laboratory investigations. The standard tests of serial electrocardiograms and serum enzyme determinations are adequate in most patients, but in some the diagnosis remains in doubt.

Thallium 201 myocardial imaging at rest has been proposed as a useful procedure in patients with suspected acute infarction.[86] Infarcted myocardium characteristically appears on the rest ^{201}Tl image as an area of moderately to substantially reduced tracer uptake in the left ventricular wall (Figure 3). The demonstration of such an abnormality, however, does not differentiate between acute and old infarction. Rest ^{201}Tl image abnormalities are also seen in some patients with (1) unstable angina,[87] (2) stable angina,[88] (3) acute myocardial ischemia,[89] and (4) coronary artery spasm.[90,91] It may be possible to differentiate infarction and ischemia by the reversibility of the ischemic defect when the patient is reimaged some hours later[88,89]; however, there is no means of differentiating acute and old myocardial infarction on ^{201}Tl imaging.

Figure 3.—65° left anterior oblique rest image from a patient with previous anterior myocardial infarction. There is substantially decreased tracer uptake in the anterior and apical regions.

The sensitivity of rest ^{201}Tl myocardial imaging for the detection of acute myocardial infarction is dependent both on the time elapsed from the onset of symptoms and on the size of the infarct.[92,93] In one study of 200 patients with documented acute myocardial infarction,[92] all patients studied within six hours of onset of symptoms had abnormal images, whereas only 72 percent of those studied more than 24 hours later showed image defects.

Because of the high sensitivity of studies shortly after onset of symptoms, rest ^{201}Tl myocardial imaging at the time of admission has been suggested as a means of selecting patients with chest pain for the coronary care unit (CCU).[94] To implement such a policy would require constant availability of the radioactive pharmaceutical agent and either a mobile gamma camera or one permanently situated in the CCU or emergency room. In addition, the patient would have to be seen within six hours of the onset of symptoms—and many patients have a longer delay than this before admission to hospital.[95] Thallium 201 imaging, therefore, is not an appropriate screening test for admission to CCU in many hospitals.

The reduced sensitivity of imaging more than 24 hours after the onset of symptoms is due principally to failure to visualize smaller, usually subendocardial, infarcts.[92,93] If sequential imaging of myocardial infarcts is done (using repeated doses of ^{201}Tl), the image defect is often larger on the study at less than six hours compared with that seen on the image made 24 hours to a week later.[92] The decrease in size of the defect with time presumably reflects resolution of peri-infarctional ischemia and edema. Detection by myocardial imaging of small infarcts in the early stages of evolution may, therefore, depend on reversible

peri-infarctional changes; late imaging fails to show the infarct because it is too small to be detected with the somewhat limited resolution available with ^{201}Tl.[96] The decreased sensitivity of late imaging and the nonspecificity of a defect for acute infarction are important shortcomings when ^{201}Tl imaging is used to attempt to clarify equivocal or conflicting ECG and enzyme studies: an abnormal image does not necessarily indicate acute infarction while a normal image does not absolutely exclude acute infarction.[93]

Thallium 201 myocardial imaging has been proposed as a means of localizing and measuring the extent of acute myocardial infarctions, factors which are related closely to a patient's prognosis. A clinicopathologic study of 23 patients who died of complications resulting from acute myocardial infarction within a few days after the ^{201}Tl imaging disclosed a slightly better correlation between postmortem location of the infarcts and findings on myocardial images than between postmortem evidence and ECG's.[97] This investigation also showed a reasonable correlation between infarct size at postmortem and the size estimated from the thallium 201 studies. In another series,[98] there was good correlation between estimation of infarct size from ^{201}Tl images obtained in the first 12 hours after symptoms and that estimated from serial serum creatinine phosphokinase measurements. However, as noted above, the size of the ^{201}Tl image defect tends to decrease in the days after the myocardial infarction.[92] Similar findings have been described in patients with acute infarctions imaged with nitrogen 13 ammonia[99] and in dogs with experimental myocardial infarction imaged with ^{201}Tl.[100] Therefore, the clinical reliability of measuring the size of acute infarcts from ^{201}Tl images is dubious, and it is unlikely that the technique will be accurate enough to judge the effect of therapies aimed at limiting infarct size. In the longer term, the ^{201}Tl image may have some prognostic value by indicating the amount of viable myocardium remaining, and in groups of patients with prior myocardial infarction, abnormalities seen on the rest myocardial scintigrams correlated well with the extent of wall-motion abnormalities at ventriculography.[69,101,102] Once again, some caution is necessary as rest image abnormalities do not always indicate earlier infarction.[88,89,102] Also, data from serial studies with rubidium 81 from 1 to 510 days after acute infarction[103] show a decrease in the size of the image defect in the late postinfarction period, possibly as the result of fibrotic shrinkage of the scar tissue.

Angina and atypical chest pain. The widest clinical application of ^{201}Tl myocardial imaging has been in the study of patients with angina

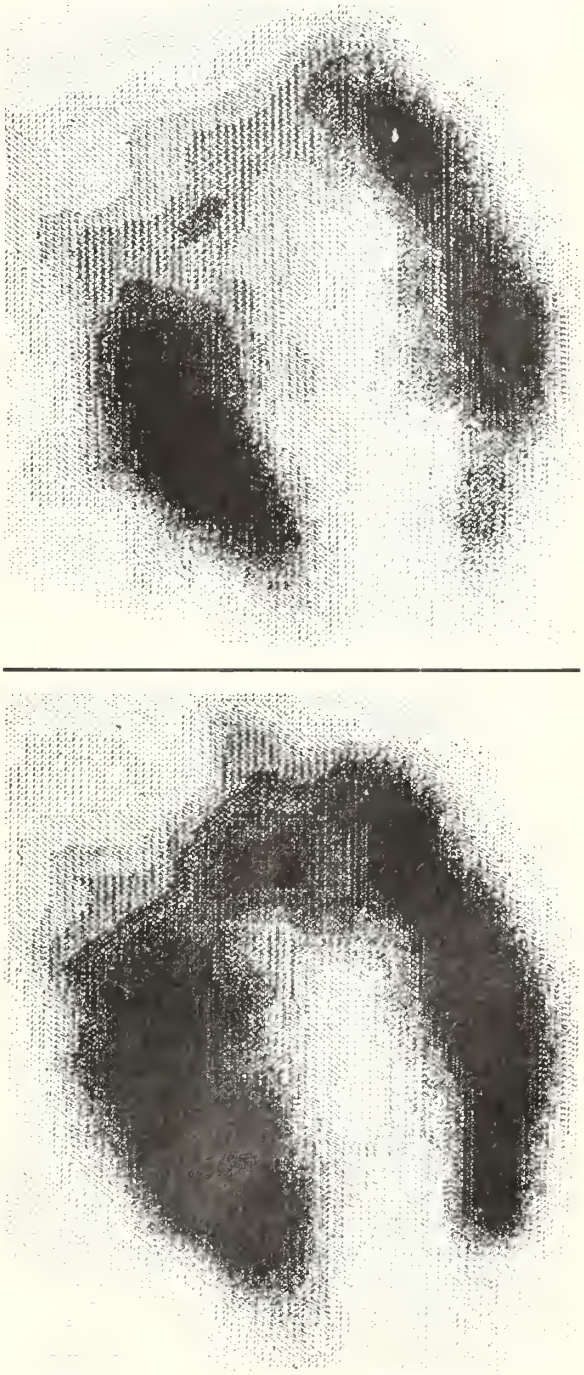

Figure 4.—Anterior images from a patient with previous myocardial infarction. The apico-inferior defect on the stress image **(above)** does not change signficantly on the rest image **(below).** A fixed defect of this type is characteristic of myocardial scarring.

pectoris or atypical chest pain. In such patients the usual procedure is to carry out a stress study first. If this is normal, then, ordinarily, no further studies are carried out. If the stress images are abnormal, they are compared with either rest images or images obtained some hours (usually about four) after the stress injection (redistribution study). Improvement of the image abnormality either at rest or on the redistribution study suggests myocardial ischemia while absence of change is usually interpreted as myocardial scarring. Figure 4 shows a "fixed" defect due to previous infarction and Figure 5, a reversible abnormality produced by myocardial ischemia.

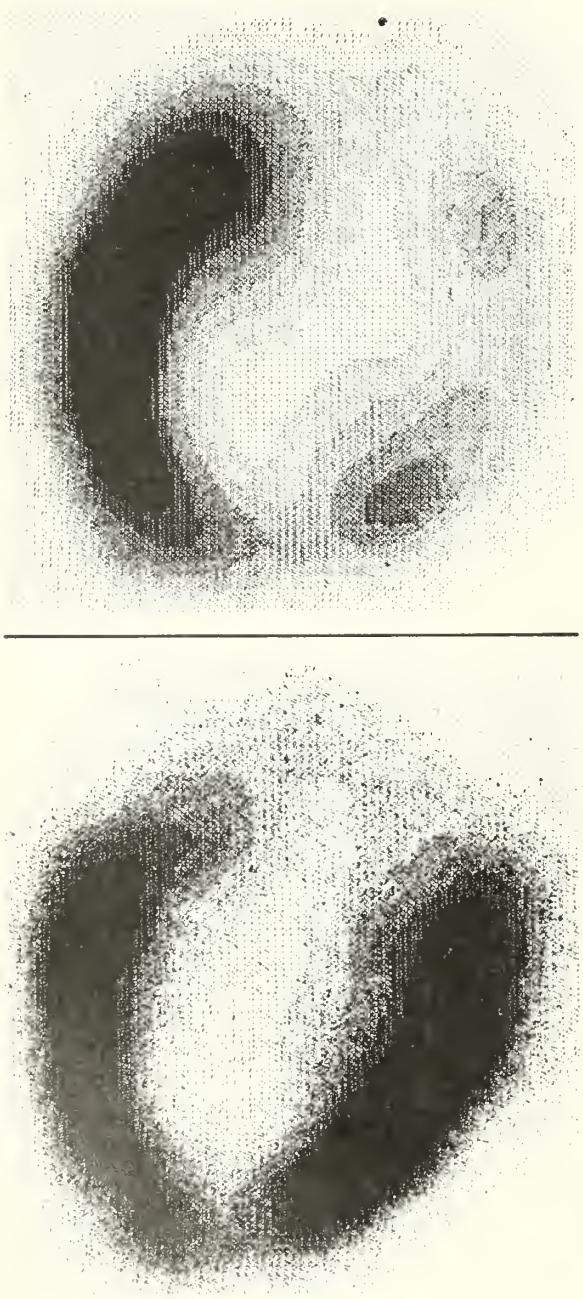

Figure 5.—45° left anterior oblique images from a patient with exertional angina. There is a pronounced posterolateral abnormality on the stress image **(above)**, which has completely reversed on the rest image **(below)**. These appearances suggest ischemia in the territory of the left circumflex coronary artery which was significantly stenosed at arteriography.

As discussed above, some caution is needed in interpreting rest image abnormalities as showing myocardial scarring, particularly when they are associated with ventriculographic evidence of normal or only slightly abnormal left ventricular wall motion.[88,102] In such patients, re-imaging two to four hours after the rest injection may be valuable as a means of differentiating more accurately between infarction and ischemia.[88]

There is some debate at present as to whether the redistribution technique[57] yields the same information as rest imaging. If it did so, only one injection of ^{201}Tl would be necessary, with both financial savings (of approximately $200) and decrease in radiation dosage for the patient. However, several recent publications have suggested that in at least a proportion of patients the two studies are not identical.[104-106] Figure 6 illustrates a study showing differences between rest and redistribution images.

Blood and co-workers[104] have reported that in 62 patients with coronary artery disease, 16 showed defects on redistribution images which were not present on the rest images. Of these patients, 11 had evidence of previous transmural myocardial infarction. They concluded that redistribution studies were more sensitive than rest images for detecting previous myocardial infarctions, especially of the inferior wall. Ritchie and colleagues[105] found discrepancies between the rest and redistribution images in 12 of 27 patients with coronary artery disease. However, they were unable to correlate the differences with presence of earlier infarction, disturbances of regional wall motion or severity of coronary stenosis. They concluded that while some redistribution occurred in most patients with exercise-induced defects, the use of the redistribution image may lead to overestimation of the extent of previous infarction. Verani and co-workers[106] found that there was a considerable overlap in redistribution scintigrams in patients with coronary disease with and without previous infarction, with a high incidence of stress-induced hypoperfusion both in infarcted and non-infarcted myocardium. They also found that good

quality collateral vessels allowed redistribution even to some areas of previous infarction.

Until the controversy over the significance of the redistribution image is resolved, it seems reasonable to carry out separate rest studies in patients who have persistent abnormalities on their redistribution scintigrams, especially if there is no history of previous infarction.

Numerous series have now been published on the sensitivity and specificity of ^{201}Tl myocardial imaging for the detection of angiographically proved coronary artery disease in patients with chest pain.[36,71,107-121] Some results are summarized in Table 1. The sensitivity of ^{201}Tl imaging for detecting significant coronary artery disease ranges from 68 percent to 100 percent, with most recent series giving figures of 75 percent to 90 percent. Comparison between different series is difficult, but factors producing the differences in sensitivity may include (1) differing criteria for the severity of stenoses considered significant, (2) whether the sensitivity reported represents only "new" lesions

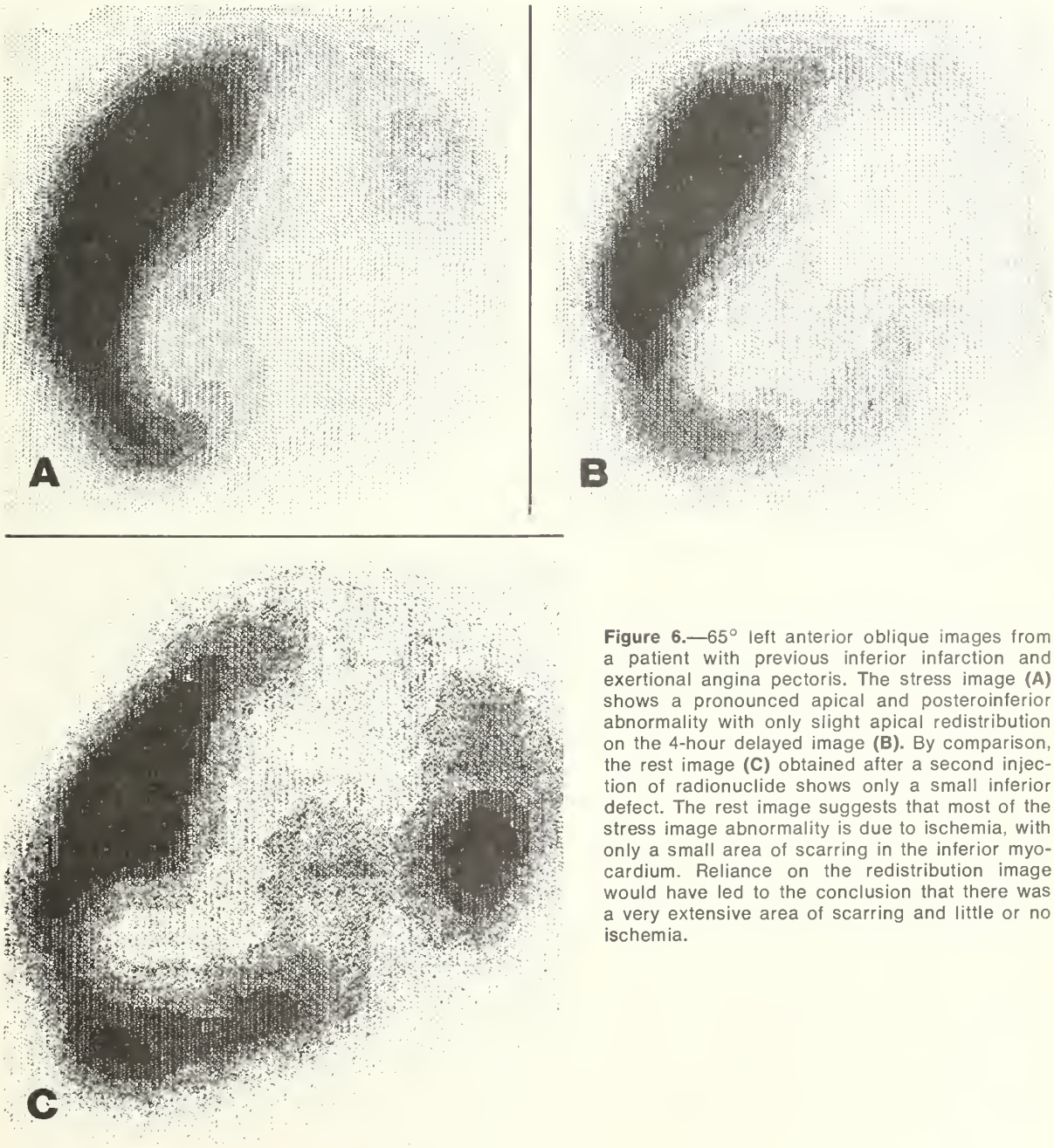

Figure 6.—65° left anterior oblique images from a patient with previous inferior infarction and exertional angina pectoris. The stress image **(A)** shows a pronounced apical and posteroinferior abnormality with only slight apical redistribution on the 4-hour delayed image **(B)**. By comparison, the rest image **(C)** obtained after a second injection of radionuclide shows only a small inferior defect. The rest image suggests that most of the stress image abnormality is due to ischemia, with only a small area of scarring in the inferior myocardium. Reliance on the redistribution image would have led to the conclusion that there was a very extensive area of scarring and little or no ischemia.

seen at stress or also includes those which do not change between rest and exercise, (3) differences in patient populations; for example, the proportion of patients with multiple-vessel disease or with good collateral circulation may be important, and (4) the method of analysis of the scintigrams. As discussed above, there is some preliminary evidence that various forms of image processing may influence the sensitivity. When particular vessels are considered, the sensitivity of detection is greatest for left anterior descending artery disease and lowest for left circumflex vessel disease.[36,117]

The specificity of thallium 201 imaging for the detection of coronary artery disease has been of the order of 80 percent to 100 percent, though a few series have produced much lower figures. The false-positive results are probably due to several factors. For instance, the criteria adopted for judging abnormalities of the images vary in different centers as does the method of processing. Use of flat background subtraction may cause a reduction in specificity.[61,62] Also, because myocardial thallium uptake is dependent on regional sodium-potassium pump function as well as myocardial blood flow, any myocardial pathology may produce an abnormal image. Such abnormalities are usually present on the rest image, but reversible "ischemic"-type defects can also be seen occasionally in noncoronary disease.[122,123]

In several studies ^{201}Tl imaging has been compared with electrocardiography. Most series (for example, see references 108, 112, 116, 124) have found myocardial imaging to have a higher sensitivity than ECG's for detecting coronary artery disease, though not all authors agree on this point.[114] Specificity for the two techniques was not significantly different in some series,[112,114] but others have indicated increased specificity for radionuclide imaging.[106,117] It has been reported in three studies[119-121] that the results of myocardial imaging are normal more frequently than those of electrocardiography in patients with chest pain and normal coronary arteriograms. Berman and colleagues[125] carried out myocardial imaging in 21 asymptomatic subjects with positive stress ECG's. The ^{201}Tl images were abnormal in six of seven patients with coronary artery disease and normal in all 14 with normal arteriograms.

The relationship between the extent of coronary artery disease and the findings on thallium 201 imaging has also received some attention. Wainwright and co-workers[115] reported a high degree of accuracy in predicting the extent of disease from myocardial images while Weisberger[126] reported a specific scintigraphic pattern for left main stem disease. Massie and colleagues[110] concluded that stress perfusion scintigraphy was a useful adjunct in identification of patients with high-risk coronary artery disease. By contrast, some of the earlier studies, without giving exact details, commented on a generally poorer correlation between the ^{201}Tl image and the coronary arteriogram in patients

TABLE 1.—*Sensitivity and Specificity of Thallium 201 Myocardial Imaging and Electrocardiography for Detection of Coronary Artery Disease in Patients With Chest Pain Who Had Undergone Coronary Arteriography**

		Thallium 201 Imaging		*Electrocardiography*		
Reference No.	*No. of Patients*	*Sensitivity Percent*	*Specificity Percent*	*Sensitivity Percent*	*Specificity Percent*	*Comments*
35	85	97	71	59	64	.....
70	46	96	90	81	65	.....
107	83	75	100	65	100	.....
108	65	85	89	67	63	.....
109	70	95	93	..	..	.....
110	32	97	..	66	..	All 2- or 3-vessel disease
111	161	88	..	..	..	.....
112	101	91	96	65	84	.....
113	22	93	86	..	..	.....
114	75	68	97	71	79	No patients with previous myocardial infarction
115	111	99	56	55	..	.....
116	95	75	91	71	86	.....
117	50	91	83	76	..	.....
118	190	78	88	..	..	Multicenter study
119	55	84	85	76	52	.....
120	53	..	91	..	77	Patients with chest pain and normal coronary angiography
121	9	..	100	..	44	Patients with chest pain and normal coronary angiography

*Sensitivities and specificities quoted are calculated from rest or exercise abnormalities, or both, where this information is available.

with multiple-vessel disease compared with patients with single-vessel disease,[109,113] while Rehn and co-workers[111] felt that myocardial imaging was sensitive but not specific in detecting left main artery disease. Three recent studies[127-129] have commented on the frequent underestimation of the extent of disease when predictions are made from myocardial images in patients with multiple-vessel disease.

The discrepancy found in many patients between estimates based on ^{201}Tl imaging and the arteriographic extent of disease may have several causes. First, coronary arteriography is open to some error of interpretation,[130] although when arteriography is compared with postmortem findings, the arteriography will underestimate more often than overestimate the extent of coronary artery disease.[131,132] Second, the presence of an anatomic stenosis at arteriography does not necessarily imply distal abnormal flow and ischemia. Two studies[17(pp84-142),133] have suggested that the presence of collateral circulation to the territory of an abnormal vessel reduces the likelihood of a radionuclide image abnormality in that region, if the area has not been the site of previous infarction. The same two studies have also shown that the differing severity of individual stenoses in multiple-vessel disease may also be important, with image defects developing only in the territory of the most abnormal vessel.[17(pp84-142),133] This may be due to pain from ischemia in this area limiting exercise before flow becomes abnormal in the territory of a less severely occluded vessel. An alternative explanation is that although the flow in the less stenosed vessels is abnormal in absolute terms, this is not detected on a myocardial image that reflects only *relative* regional perfusion. A third factor making prediction of extent of disease from myocardial images difficult is the variability of territories of the coronary arteries, especially the reciprocal relationship between the right and left circumflex vessels.[134,135] As a result, an image defect in certain areas may represent abnormalities in the territories of one or both vessels.[128]

What then is the role of ^{201}Tl myocardial imaging in a patient with possible ischemic heart disease? The patient with classic angina pectoris and an abnormal ECG has a high probability of having coronary artery disease, and the results of myocardial imaging will not produce any significant change in this probability.[138] Myocardial imaging, therefore, has very limited value as a diagnostic procedure for coronary artery disease in this group of patients. Patients with abnormalities on the myocardial scintigrams that suggest multiple-vessel disease, usually have more than one abnormal vessel at arteriography, but as noted above, the extent of disease is often underestimated from the myocardial images. Therefore, high-risk coronary disease may be suggested from ^{201}Tl images, but cannot be excluded by them. Thallium 201 imaging is thus not reliable in identifying patients who require more invasive studies as a prelude to possible coronary artery operations. The findings on rest myocardial imaging may have some prognostic value by showing the extent of irreversibly damaged (or very severely ischemic) myocardium. Similarly, the findings of only small areas of ischemic defects during stress may be a good prognostic sign by indicating single-vessel disease or multiple-vessel disease with good collateralization. These prognostic points, however, remain speculative at present. Finally, preoperative myocardial imaging in this group of patients would be valuable when a decision has been made to carry out a bypass surgical operation. Comparison of preoperative and postoperative images may be of value in assessing the adequacy of myocardial revascularization (see below).

Thallium 201 myocardial imaging is of great clinical use in patients with various atypical chest pain syndromes which may be associated with coronary artery disease. For such patients stress myocardial imaging is usually combined with stress electrocardiography. If results of both investigations are normal, the probability of significant cardiac disease is low, and further investigation is not indicated. By comparison, if abnormal studies are obtained, further cardiac investigation should be instituted. It should be noted that while an abnormal myocardial image in a patient with atypical chest pain is most often due to coronary artery disease, it is not specific for this diagnosis and may be produced by a variety of other myocardial pathologies.

A further indication for ^{201}Tl myocardial imaging is in assessing the functional significance of coronary artery lesions which are borderline at coronary arteriography. The uptake of the radionuclide by the myocardium reflects regional small-vessel blood flow and myocardial cell function. A normal stress myocardial image in the territory of a borderline abnormal vessel suggests that the stenosis is not of hemodynamic significance. By

comparison, a reversible stress image abnormality in that territory is an indication that the occlusive lesion is producing regional myocardial ischemia.

A major indication for myocardial imaging is in the clarification of equivocal ECG changes in patients with atypical chest pain or the presence of abnormal ECG findings in asymptomatic subjects.[139] Normal stress images considerably reduce the probability of coronary artery disease in such patients and, depending on the clinical setting, may obviate the need for further investigation. Myocardial imaging is also very valuable in a patient whose stress ECG cannot be interpreted; for example, because of digoxin effect or left bundle branch block (LBBB). The finding of a reversible stress image abnormality is highly suggestive of ischemic heart disease. The significance of rest image abnormalities in patients with LBBB is less clear. Studies using ^{43}K and ^{81}Rb showed septal abnormalities at rest in patients with LBBB and no coronary disease.[136] By contrast, in patients with suspected acute myocardial infarction and LBBB, rest ^{201}Tl image abnormalities occurred only in those patients subsequently shown to have acute infarction.[137]

Because of the high cost of the test, the sensitivity and specificity obtained and the low yield to be expected, it is unlikely that myocardial imaging will be a suitable screening test for coronary artery disease in large asymptomatic populations.[138] Myocardial imaging may be useful, however, as a noninvasive screening test both at the time of presentation and during follow-up of patients with known high-risk factors for coronary atherosclerosis, such as hyperlipidemia.

After coronary artery bypass operations. Myocardial imaging has been used as a method of assessing the adequacy of myocardial revascularization after a coronary artery bypass operation. When comparing myocardial imaging and postoperative arteriography, it is important to remember that myocardial revascularization and anatomic graft patency are not necessarily synonymous.[140] Thus, a patent graft may supply an area of myocardial infarction[141] which would appear abnormal on the myocardial image. Similarly, collaterals to the grafted vessel from nondiseased vessels may develop after the operation,[142] and it is possible, at least theoretically, that this might maintain myocardial perfusion in spite of proximal graft occlusion.

The success of showing improved myocardial perfusion after an operation using potassium 43,[143] and rubidium 81[144] has been followed by similar applications of thallium 201 imaging.[113,145-152]

Overall, postoperative improvement in stress myocardial images has been associated with a high frequency of graft patency.[145-148] Rest myocardial images may also improve following a bypass procedure, especially in segments not associated with Q waves on ECG.[151] Similarly, abnormalities present on postoperative stress images correspond well to incomplete revascularization, either due to graft occlusion or to disease of ungrafted vessels.[144,146,147,150] One must be cautious in interpreting apical abnormalities because in some patients after operation there may be apical defects more pronounced than normal thinning without coronary occlusion, perhaps due to insertion of a vent into the apex of the left ventricle during the operation.[17(pp149-163)] It should be noted that absence of improved results on myocardial imaging after the operation does not preclude alleviation of angina and increased exercise tolerance.[149] Although overall correlation between improvement or continued abnormal findings on the postoperative scintigram and arteriogram is fair, prediction of occlusion or patency of individual grafts or ungrafted vessels has been less successful in several series.[145,146,148,150,152] The ability to predict the patency of individual grafts is improved if there is an abnormality in that vessel's territory on the preoperative study.[152]

Because of the limitations of ^{201}Tl imaging in predicting the status of individual grafts, its main value in the postoperative assessment of a patient who has had good symptomatic relief is to serve as a baseline for future comparison. If, however, the patient continues to have chest pain after the operation, the presence of abnormal findings on the scintigram is highly suggestive of incomplete revascularization. By comparison, the conversion of an abnormal preoperative to a normal postoperative study indicates that the pain is more likely to be noncardiac in origin.

Variant angina. Myocardial ischemia due to coronary artery spasm is associated with reduction in myocardial perfusion, which can be shown by ^{201}Tl imaging.[90] Images obtained during a spontaneous attack show transmural reduction in ^{201}Tl uptake in the affected myocardial territory, with reversal of the abnormality on redistribution images or on separate rest images obtained when the patient is free of pain.[90] Similar reduction in ^{201}Tl uptake can be shown when attacks are induced pharmacologically in affected subjects through adminis-

tration of ergonovine maleate.[36,90,91,153] Thallium 201 myocardial imaging after the patient has been given this drug is a useful means of showing the effect of coronary spasm on myocardial perfusion and metabolism, and may be a method of assessing the value of proposed therapies. However, because of the danger of inducing spasm in patients with arteriosclerotic coronary disease, such provocative tests should be carried out only after fixed coronary occlusion has been excluded by standard rest and exercise myocardial imaging or by coronary arteriography.

Noncoronary Disease

Valvular heart disease. Thallium 201 myocardial imaging has been applied in patients with aortic valve disease to determine whether they also have coronary artery disease, because this has important prognostic and therapeutic implications. Two studies, the first including patients with pure aortic stenosis[154] and the second including some patients with aortic stenosis and others with combined aortic stenosis and regurgitation,[155] have shown that in patients with these conditions, abnormal stress myocardial images can be obtained in some patients with no significant coronary artery disease while a normal image does not exclude obstructive coronary disease. The false-negative studies may be related to the patient's exercise capacity being limited by low cardiac output before myocardial ischemia develops.

The explanation for positive studies in patients without coronary disease is unclear. Similar false-positive studies in cases of aortic stenosis have been recorded with ^{43}K.[122] It does appear, however, that potassium analog myocardial imaging cannot be used to exclude or to confirm the presence of occlusive coronary disease in patients with aortic valve disease.

Mitral valve prolapse may be accompanied by atypical chest pain, false-positive electrocardiograms and arrhythmias, and may thus mimic coronary disease. Thallium 201 imaging has been investigated in this group of patients.[156-159] The weight of evidence in the literature suggests that the technique is valuable in differentiating patients with prolapse who have coronary disease from those who do not, abnormal results on scintigrams being found only in the former group.

Nonischemic cardiomyopathy. Although myocardial imaging has proved most useful for studying coronary artery disorders, it has also been applied to certain noncoronary cardiomyopathies.[65,122,123,160-163] The myocardial images usually have a nonspecific appearance in noncoronary cardiomyopathy and do not usually help in distinguishing the cause.[163] Rather, they show the effect of the disease process on myocardial anatomy and function, and can be used in assessing whether hypertrophy or dilatation of either ventricle is present.[65,122,163] Focal abnormalities appearing during stress are not entirely specific for occlusive coronary artery disease and may also be seen occasionally in patients with noncoronary cardiomyopathy.[122,123,164]

A more specific pattern of abnormality has been reported in idiopathic hypertrophic subaortic stenosis (IHSS), where the ratio of thickness of the septum to that of the free left ventricular wall exceeds 1.7.[160] In addition, the posterior left ventricular free wall is thicker in the obstructive compared with the nonobstructive form of the disease.[160] Patients with IHSS may show stress-induced focal defects of ^{201}Tl uptake in the absence of significant coronary disease.[164] It should be noted, however, that the noninvasive diagnosis of IHSS, and left ventricular hypertrophy in general, is best made from the ECG and echocardiography rather than from ^{201}Tl imaging.

Focal myocardial image abnormalities at rest are found in patients with myocardial sarcoid granulomata, and this study may be a useful means of differentiating cardiac dysfunction due to cor pulmonale from that resulting from direct myocardial involvement.[161] In a recent study myocardial image abnormalities were reported in almost a third of 50 patients with sarcoidosis who did not have cardiovascular symptoms.[162]

Miscellaneous conditions. Visualization of the right ventricle on rest ^{201}Tl images may occur in acute pulmonary embolism.[163] As noted earlier,[74,75] chronic pulmonary hypertension and right ventricular hypertrophy result in visualization of the right ventricle on rest images.

Thallium 201 imaging is possible in neonates and young children and can be used to differentiate global "transient myocardial ischemia" from focal ischemia resulting from an anomalous left coronary artery.[165] Myocardial imaging can also be used to assess myocardial perfusion following surgical intervention for an anomalous left coronary artery.[166] Thallium 201 imaging has also allowed successful differentiation between tetralogy of Fallot and single ventricle disease.[66]

Finally, it may be possible to recognize the presence of pericardial effusion from a halo of sub-

stantially decreased background activity around the heart on rest myocardial images.[163]

Noncardiac Applications of Thallium 201 Imaging

The whole body distribution of ^{201}Tl following intravenous injection parallels regional blood and regional metabolic activity, and the fractional distribution of the isotope has been suggested as a method of studying the regional distribution of cardiac output.[167] This approach has been questioned because of the many factors other than regional blood flow that might alter the distribution of ^{201}Tl.[168] Imaging of the lower limbs after injection of ^{201}Tl at rest and during exercise has been done in patients with peripheral vascular disease, and has been proposed as a method of studying the functional result of major vessel occlusion.[169]

In addition to metabolically active normal tissues, ^{201}Tl has been found to accumulate in certain pathological tissues. Cox and colleagues[170] reported an abnormal concentration of ^{201}Tl in the primary tumor of a man with bronchial carcinoma. They also showed that the nuclide was taken up by rhabdomyosarcoma implants in rats. Tonami and associates[171] investigated ^{201}Tl as a tumor-imaging agent in humans. They found abnormal uptake of the isotope in 14 of 15 patients with hepatomas but in none of 8 with hepatic metastasis. In patients with thyroid nodules, 14 of 15 with thyroid cancer had a hot spot on ^{201}Tl imaging, whereas in only 6 of 19 patients, benign adenomas which were "cold" on technetium 99m imaging concentrated ^{201}Tl. The same group have also reported ^{201}Tl uptake in primary lung and esophageal carcinomas.[172] Thallium 201 uptake has also been recorded in single cases of lymph node metastasis from thyroid carcinoma,[173] in a benign parathyroid adenoma[174] and in two cases of subacute thyroiditis.[175]

Conclusion

Thallium 201 myocardial imaging, though a relatively new technique, has been the subject of extensive evaluation. Its clinical use in several situations is still unresolved, but the following indications for carrying out the procedure are now generally accepted:

- The study of patients with symptoms suggestive of coronary artery disease, especially those with atypical chest pain or ECG findings that are equivocal or cannot be clearly interpreted. (Its value in identifying patients with high-risk coronary disease remains controversial.)
- The clarification of the significance of an abnormal ECG discovered during routine screening of an asymptomatic subject.
- The assessment of the hemodynamic significance of a borderline lesion seen at coronary arteriography.
- The follow-up of patients after coronary artery bypass operations.
- The exclusion of coexistent coronary disease in patients with mitral valve prolapse—thallium 201 imaging cannot be used to confirm or exclude coronary disease in aortic valve disease.
- A normal myocardial image obtained in the few hours after the onset of acute chest pain virtually excludes acute myocardial infarction. Studies delayed beyond this time are less valuable, and there are difficulties in using the technique to quantitate infarct size accurately.
- Thallium 201 imaging in patients with possible variant angina due to coronary artery spasm.
- The noninvasive detection of right ventricular hypertrophy.

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Specialty Conference

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Cavernous Sinus Thrombosis

MARY ZAHLLER, MD:* An 11-year-old boy was brought to the emergency room with pronounced swelling of the right eye and a temperature of 41.1°C (106°F). He seemed disoriented. He had been well until two days previously when a "stye" had developed on the right upper eyelid. The boy's eye had been treated at home with applications of hot compresses. He had no systemic symptoms until four hours before admission when he began to feel warm and fatigued, and he went to bed. Three hours later his mother had difficulty awakening him. She noted a definite difference in his facial appearance: the periorbital region on the right side was extremely swollen, and there was pain and tenderness of the right globe.

His past medical history included three major medical problems: episodes of occasional wheezing, which had been treated intermittently with bronchodilators; four generalized seizures, all of which were associated with fever; and frequent headaches, commonly accompanied by vomiting. There was no history of recurrent infections, abscesses or fevers. The patient was receiving no regular medications and there was no recent history of trauma to the eye or head.

On physical examination the patient appeared acutely ill, with episodes of restlessness alternating with lethargy and flaccidity. Temperature was 41.1°C (106°F), pulse 102 beats per minute, respirations 24 per minute and blood pressure 90/68 mm of mercury. The neck was notably stiff to passive flexion. The ophthalmic findings will be discussed by Dr. Spector.

ROBERT H. SPECTOR, MD:* Visual acuity was difficult to assess in either eye. The patient responded to a bright light by wincing away from the stimulus. The right nasolabial fold was flatter than the left, and the right eye was substantially proptotic (Figure 1). There was edema of the upper and lower lids and injection of the scleral vessels. A 3 by 3 mm crusted lesion was visible on the right upper eyelid. The right pupil reacted only sluggishly to light, and the right eye moved minimally in all directions. The funduscopic appearance of the right retina was unremarkable. The left eye was entirely normal at this time, including motility, lid function, pupillary reactivity and funduscopic appearance.

DR. ZAHLLER: Results of an ear, nose and throat examination were within normal limits. Findings of an examination of the chest, heart and abdomen were unremarkable. The patient was unable to cooperate but moved all extremities in a symmetric manner. The knee, ankle and biceps jerks

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were not elicitable. Both plantar responses were extensor. Kernig and Brudzinski signs were positive. The remainder of the physical examination showed no abnormalities. A lumbar puncture was immediately done. The cerebrospinal fluid (CSF) contained 1,240 leukocytes per cu mm, of which 80 percent were polymorphonuclear forms. The CSF glucose concentration was 76 mg, concomitant serum glucose 151 mg and protein 167 mg per dl. The Gram stain was negative.

Ampicillin, chloramphenicol and oxacillin were administered immediately. Two hours after admission the boy's left eye, which had previously been normal, became proptotic (Figure 1), and the patient was unable to abduct the eye either on command or following cold-water caloric stimulation of the left ear. The right eye had complete pupillary areflexia and paralysis of the external ocular muscles and lid. A cavernous sinus thrombosis of septic origin was suspected. Treatment was begun with 5 mg of dexamethasone every six hours along with 600 mg of acetylsalicylic acid every four hours. Roentgenograms of the sinuses and routine skull films showed no abnormalities. However, a roentgenogram of the chest showed several fluffy infiltrations consistent with septic emboli.

The patient's level of consciousness improved in a few hours and the swelling of both eyes decreased over the next 12 hours. The limitation of motility of the left eye also improved from complete to partial ophthalmoplegia in all directions of gaze. Some 24 hours after the initiation of antibiotic therapy, movements of both eyes had improved further (Figure 2). The patient remained restless and febrile. A radioisotope scan of the brain was normal. Electroencephalography showed diffuse changes consistent with diffuse encephalopathy.

Acetylsalicylic acid and dexamethasone were discontinued after 48 hours because of the development of guaiac-positive emesis and stool. Two blood cultures obtained at the time of admission and a culture of the lesion of the right eye grew coagulase-positive *Staphylococcus aureus,* which was resistant to penicillin. Cultures of the cerebrospinal fluid were negative. Ampicillin and chloramphenicol were discontinued and treatment with 1,500 grams of oxacillin every six hours was maintained.

By 48 hours after admission the patient was cooperative and the visual acuity in each eye was measured at 20/20. He remained intermittently febrile, with temperature elevations reaching 38.9°C (102°F) each day. A repeat x-ray study of the chest showed cavitation of the three lesions seen on admission. Repeat cultures of the blood were negative. A radioisotope scan of the bones was normal. Seven days after admission there was only moderate ptosis of the right eye and mild paresis of the abductor and the superior oblique muscles. The motility of the left eye was entirely normal. There was no further emesis, but guaiac-positive stools continued for another week. The hematocrit fell to a low of 30 percent ten days after admission, but a transfusion was not required.

Computerized tomography (CT) was carried out using contrast material on hospital day 15 (Figure 3). There was a distinct area of increased density along the right hippocampal gyrus. Because of persistent fever and the findings of the CT scan, therapy with chloramphenicol was reinstituted. Complete defervescence occurred 16 days following admission.

The patient was diagnosed as having cavernous

Figure 1.—Proptosis of the right eye and bilateral edema of the eyelids.

Figure 2.—Appearance 24 hours after initiation of antibiotic therapy. Bilateral chemosis; the right eye could not abduct, while the left eye was clearly in abduction.

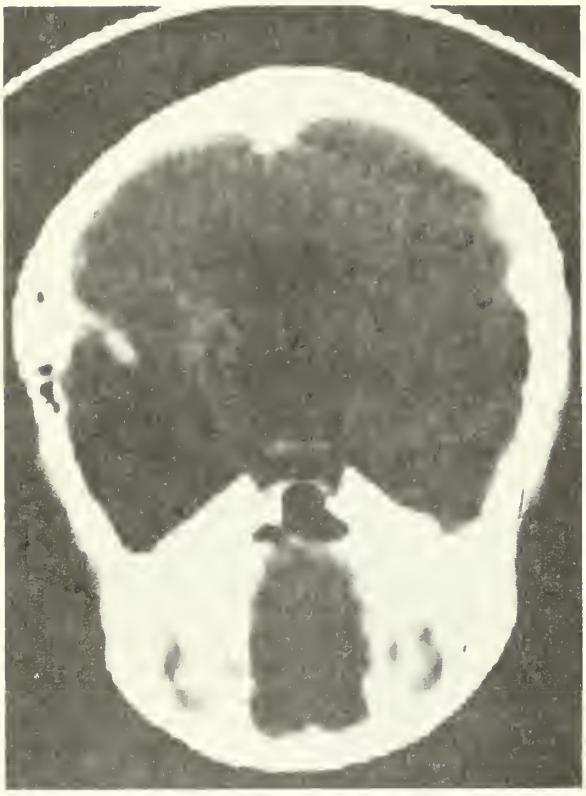

Figure 3.—A computerized tomographic scan of the head on day 15, showing increased density in the right hippocampal area.

sinus thrombosis. He responded very favorably to treatment. On the third day of the illness, an examination of the eyes showed no abnormalities other than a mild weakness in abduction of the right eye and minimal ptosis. At the most recent follow-up examination, the boy's extraocular movements showed no residual abnormality. Vision was normal bilaterally, although he had evidence of a mild hemiparesis. His favorable response to treatment indicated that he did not have an immunologic disorder. He showed a normal immune response as indicated by his leukocytosis.

Anatomy

CAPT R. R. SKOGLUND, MC, USN:* In considering the problem of cavernous sinus thrombosis it is useful to review the relevant anatomy. The dural sinuses are venous channels for the brain. They contain no valves and are located between the inner and outer layers of the dura. The cavernous sinuses are expanded trabeculated venous sinuses that lie on either side of the pituitary fossa. The right and left cavernous sinuses are interconnected by a rich network of venous channels called the intercavernous or circular sinus. Each of the cavernous sinuses represents the primary venous reservoir and outflow conduit for blood transversing the superior and inferior ophthalmic veins, some of the cerebral veins and the sphenoparietal sinus. There is communication with the transverse sinus through the superior petrosal sinus and with the ocular and facial venous systems. The cavernous sinus houses several important structures: the oculomotor, trochlear, ophthalmic and maxillary nerves are embedded in its lateral wall; and the internal carotid artery with its sympathetic plexus and the abducens nerve pass through the sinus close to its medial wall. Each of the cranial nerves occupies a separate fiber sheath which separates it from the venous blood which transverses the sinus.

Thrombosis of the cavernous sinus produces a variety of ocular and neurological signs. The former include proptosis and edema of the lids and conjunctivae. Involvement of cranial nerves results in paresis of cranial nerves III, IV and VI. Sometimes, the first and second divisions of cranial nerve V are also involved, and there may be oculosympathetic paralysis as well. The pupil may be small and immobile as a consequence of combined oculomotor parasympathetic and sympathetic denervation.

The circular sinus permits free communication between the right and left cavernous sinuses, and this accounts for bilateral symptomatology. In the case described there was a typical course of events in thrombosis of the cavernous sinus. It is likely that the stye of the eyelid formed the original nidus of infection. The draining superior ophthalmic vein emptied septic material into the cavernous sinus, and the consequent neuro-ophthalmologic syndrome developed ipsilaterally. Hours later the contralateral globe and extraocular musculature became involved. At the height of his illness, the boy had bilateral edema of the eyelids and conjunctivae, bilateral internal (pupil) and external ophthalmoparesis and signs of systemic infection.

As the symptoms and signs of cavernous sinus thrombosis resolved, a computerized tomographic scan of the brain uncovered radiological signs suggesting a brain abscess in the hippocampal area. We propose that infected material exited the

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cavernous sinus into the draining superior petrosal sinus and produced a parameningeal lesion.

Discussion

Cavernous sinus thrombosis was first recognized in about 1821. Throughout the 19th century it was reported as a disorder with a catastrophic outcome. It was not until the 1930's that the first survivors were reported following the use of sulfa drugs. Earlier literature reported an 80 percent mortality, with 75 percent of the survivors having significant residual injury.[1] In 1970 a small series reported a mortality of 28.6 percent.[2] In 1977 the most recent series of cases to be reported gave the best outcomes to date: mortality was 13.6 percent and morbidity 23 percent.[3]

Certain sequelae may arise from damage to the cavernous sinus and inflammation surrounding the area. One of these is brain abscess, which was a potential complication in our patient. The CT scan showed a small circumscribed area of lucency that seemed to form a circular pattern in the medial right temporal region. It is not clear whether this represents a stroke pattern or evidence of a nonedematous abscess wall. The proximity of the pituitary gland and reports of fatal pituitary necrosis prompted the early use of steroid treatment. Thus, the use of steroids was not solely for their antiinflammatory properties.

The decrease in mortality for this condition can be related to treatment with antibiotics. There are arguments as to whether anticoagulation therapy may be useful. On the other hand, treatment of cavernous sinus thrombosis with anticoagulants may lead to hemorrhage. We decided to avoid that prospect in the patient, in whom there was pleocytosis of the CSF. Acetylsalicylic acid was administered in low doses in order to interfere with platelet function and to avoid progression of thrombus. Good hydration was maintained, despite the usual policy of restricting fluids in patients with intracranial infections. Antibiotics in high dosage completed the medical regimen. The nature of the disease as well as the possibility of abscess in the brain and lung dictated the use of antibiotic therapy for four weeks.

In a patient presenting with a swollen eye and fever, the differential diagnosis should include orbital cellulitis. The literature on that condition from the preantibiotic era indicated a mortality of 17 percent, with blindness occurring in about 20 percent of the affected eyes of survivors. In 1976 the case histories of some 104 patients with orbital cellulitis, ranging in age from 2 weeks to 14 years, were reviewed. About 75 percent of the patients were less than 5 years old. Roentgenograms showed sinusitis in 84 percent. The ethmoid and maxillary sinuses were the most often affected. In that series, 36 percent of patients who had not received prior antibiotic therapy had positive blood cultures. The principal organisms were *Haemophilus influenzae* type b and *Diplococcus pneumoniae*. Four of the children had concomitant meningeal signs and two had pleocytosis of the cerebrospinal fluid, with negative CSF cultures.

The differential diagnosis also should include a problem that is illustrated by the case of a little girl treated by Dr. Digby.

DONALD DIGBY, MD:* The patient presented with proptosis, a sudden loss of vision and ophthalmoplegia of the right eye. B scan ultrasonography of the orbit supported the diagnosis of orbital pseudotumor, a condition that may be confused with endocrine exophthalmos.

DR. SKOGLUND: In one survey ophthalmoplegia was present in 15 of 16 patients with orbital pseudotumor, and in all of 12 patients with endocrine exophthalmos. Thus, a restriction of extraocular movements is not diagnostic of cavernous sinus thrombosis. Pain that was indistinguishable from migraine was reported in 15 of the 16 patients in the first group but in only 3 of 12 patients with endocrine exophthalmos. Visual impairment was present in 13 of 16 patients in the first group and in 6 of 12 patients in the second. Those with orbital pseudotumor tended to have sudden visual loss with large central scotomata while those with endocrine exophthalmos tended to have a slow loss of vision.[5]

Summary

WILLIAM L. NYHAN, MD, PHD:† To summarize, we discussed the case of an 11-year-old boy with a cavernous sinus thrombosis. The onset of his illness was extremely rapid. The disorder was diagnosed promptly and treated with antibiotics as well as a short course of acetylsalicylic acid and steroids. He responded very well and, ultimately, recovered completely.

Complications observed included septicemia with *S aureus* and gastrointestinal hemorrhage. The focal lesion visualized on the CT scan again

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points up the value of that procedure. The persistent fever during 15 days of therapy is indicative of the difficulty in treating a condition in which there were probably many small collections of abscess material inaccessible to drainage. I recommend that in such cases antibiotic therapy in effective doses be continued until all inflammatory signs of disease have disappeared, including fever, leukocytosis and elevation of the sedimentation rate—and then continued for a week or two thereafter. This is more rational than continuing treatment for an arbitrary number of weeks.

Cavernous sinus thrombosis is a medical emergency. It remains a potentially lethal disease, although the development of antibiotics has resulted in an enormous improvement in lowering mortality and long-term morbidity. Current experience underscores the importance of early diagnosis as well as early institution of a vigorous therapeutic program.

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Uses of Vancomycin

WHAT IS THIS DRUG and why has it enjoyed a rebirth? . . . Vancomycin hydrochloride is a drug that has superb activity against Gram-positive organisms. Staphylococci are sensitive to this drug—not only staphylococci that make penicillinase but also those that are resistant to pencillin, as well as those resistant to methicillin, oxacillin and nafcillin. These staphylococci are also sensitive to vancomycin. So, if you want to have a drug that you know is going to work against a staphylococcus, regardless of any situation that might arise, vancomycin would be your choice. I doubt that this would often come up in private practice; nevertheless, you would not be wrong to turn to vancomycin.

The drug also works against streptococci—all streptococci are sensitive to vancomycin, including group B hemolytic streptococci. The same thing is true for enterococci organisms—they are quite sensitive to vancomycin, but . . . you cannot use vancomycin by itself to treat blood-borne enterococcal infection. In this siutation, you would have to use vancomycin and an aminoglycoside. What about *Haemophilus influenzae?* . . . Vancomycin has no activity against any Gram-negative organism, period. It is strictly a Gram-positive antibiotic.

—DAVID J. DRUTZ, MD, *San Antonio, Texas*

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Refer to: Heyneman D: Schistosomiasis: Recent developments in immunology and treatment—Medical Staff Conference, University of California, San Francisco. West J Med 133:49-56, Jul 1980

Schistosomiasis: Recent Developments in Immunology and Treatment

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *In this Medical Grand Rounds we shall discuss one of the most important diseases on an international scale, schistosomiasis, which affects the health of hundreds of millions of people. The discussant is Dr. Donald Heyneman, Professor of Parasitology.*

DR. HEYNEMAN:† Recent developments in schistosomiasis research lie chiefly in the area of immunology,[1,2] including newly discovered aspects of the role of the eosinophil.[3,4] Preliminary efforts at vaccine development and other immunization approaches accompany these studies.[5] The practical objective of disease control has as a concomitant objective the development of a useful model for other studies, such as basic research on the eosinophil, on hypersensitivity and on the process of granuloma induction.

Epidemiology of Schistosomiasis

Schistosomiasis—in its pathological features, numbers of persons it afflicts, its social impact and new dangers of its spread, especially in tropical regions—shares with malaria a preeminence in its worldwide importance. Both are part of the daily lives of more than 500 million people, with more than a million deaths annually attributed to malaria, and untold levels of suffering and underachievement of human potential from both diseases. Many people in the tropical world, especially in Africa, have one or both. Yet, they are rarely treated, owing to high cost and the problems of retreatment among continuously exposed populations. Few among these millions know what a *non*diseased state is. Therefore, it is difficult to determine with any sense of reliability the economic, as well as the social, impact of malaria and of schistosome organisms living in humans.[6] Furthermore, these parasites are reasonably well adapted to humans in spite of the high morbidity (and mortality among young children infected with falciparum malaria). Malaria probably repeatedly infects most exposed persons, but is held in check at a low level while reinfection is blocked so long as the previous infection is present (premunition). A similar partial immunity to schistosomiasis is found. The host seems unable to de-

*Lloyd H. Smith, Jr. MD, Professor and Chairman, Department of Medicine.

†Donald Heyneman, PhD, Professor of Parasitology.

stroy a current infection, but the latter stimulates the host to stop a reinfection (concomitant immunity).

With schistosomiasis, we are concerned chiefly with its long-continuing aspects—the chronic stages and advanced forms of the disease. Most infected people appear not to be grossly affected, so it is difficult to know the total impact, though it must be incalculably great. For example, among 600 million persons in Africa, South America and Southeast Asia exposed to schistosome infection, about 200 million are thought to be infected. It is difficult even to contemplate this level of infection or its cumulative tissue damage and impact on the societies affected.

Our best hope against malaria, now returning to its former levels of infection in many previously controlled areas, would be an inexpensive, nontoxic and effective prophylactic vaccine. This is, optimistically, five years away—more likely ten. Schistosomiasis, on the other hand, seems much farther from vaccine control, though this is an active research quest. First is the need to halt the spread of infection into every new water development project in endemic areas. Schistosomiasis is essentially a disease of development in the Third World. Inexpensive, oral, single-dose drugs with reduced toxicity are a crucial part of this mass therapy requirement, and progress here is encouraging. There also appears to be reason to hope that successful therapy will lead to a reversal of the chronic, cumulative course of disease. Tissue stimulation from the continuing presence and accumulation of worm eggs initiates a strong host response, leading to fibrosis and tissue damage.[7] Essentially, the disease process is an over-reactive host response to masses of worm eggs caught in the tissues.

Schistosomiasis as an Environmental Problem

Fundamentally, schistosomiasis is an environmental problem, one of special importance in the watered regions throughout Africa. This includes many desert areas where human habits and a restricted water supply concentrate both people and the elements of infection. Desert Arabs and other Moslem groups must perform cleansing ablutions before prayer. They necessarily use the same ponds that are infected by egg-bearing feces or urine of children who play and wash in these ponds. And the presence of snail intermediate hosts completes the chain of contagion. *Schistosoma mansoni* (spread from egg-bearing feces in water) is extensively distributed in Africa, the Middle East, South America and certain Caribbean islands. *S haematobium* (from infected urine in water) is widespread throughout Africa and has spread into the Middle East. *S japonicum* (via infected human feces in water) is still spreading in the Philippines, is largely controlled in Japan and is greatly reduced in vast areas of the Yangtze Valley of China, formerly the chief focus of this disease. A new form, *S mekongi* has recently been found in Cambodia, Laos, Thailand, Malaysia and Indonesia.

Schistosomiasis is spreading in many areas as new waterways and irrigation canals extend the snails' habitat. Whole irrigation schemes in Iran and Kenya have been cancelled and others threatened because of this societal as well as medical parasite. This is particularly true of the great man-made lakes of Africa, including the Aswan High Dam (forming Lake Nasser), the Kariba Dam on the Zambesi, and Lake Volta, formed by the Akasombo Dam in Ghana from the three branches of the Volta River.[8] Lake Volta is currently the largest man-made body of water in the world. All efforts to prevent and, subsequently, to control schistosomiasis in these developing areas have failed. Unless prevention of schistosomiasis can become an integral and high-priority part of initial planning for irrigation schemes in endemic areas, there is little hope for success. Snail control that begins *after* the concrete is poured is already too late.

Exposure to infective schistosome cercariae in contaminated water is unavoidable by most people in affected areas. Their sanitary habits, agricultural needs, customs of animal care, children's play and, as noted, even religious customs make it nearly impossible to prevent transmission of schistosomiasis. Water is an integral part of the daily lives of these people—and the parasite, its aquatic snail host and water for human use are inseparable. Any attempt to block transmission must focus on the most epidemiologically significant group: children 5 to 10 years old. Though they may show little indication of infection (except hematuria with *S haematobium*), these children are the chief egg passers and hence the most consistent and dangerous sources for maintenance or establishment of infection in the snail hosts.

Snail control is extremely difficult because, among other factors, these hosts are among the most hardy, widely distributed, rapidly spread

and reproductively active organisms in their aquatic habitat. Within a few months the snails can repopulate an area that was cleared of them, reestablishing colonies from eggs on the feet of aquatic birds, or snails washed in with the current or carried in dirt loads used to build the irrigation feeder canals. The snails are hermaphroditic, so a single snail can repopulate an irrigation stream, ditch, river or lake. Yet, control must not poison all forms of freshwater aquatic life and should be restricted to areas where infection is actively transmitted. Ecological, epidemiological and economic factors are all important in developing a control scheme, and each area must develop its own requirements and plan. Behavioral modification, tied to an extensive program of education that is compatible with the beliefs and the habits of the people affected is equally essential. Engineering projects designed for the most efficient and cost-effective construction plan possible almost inevitably will fail to consider their health impact. Too often economic failure as well as social disruption follow when the engineering requirements are met but epidemiological ones ignored. Schistosomiasis is an epidemiological, sociocultural, and economic, as well as medical concern involving some 200 million people and affecting many others.

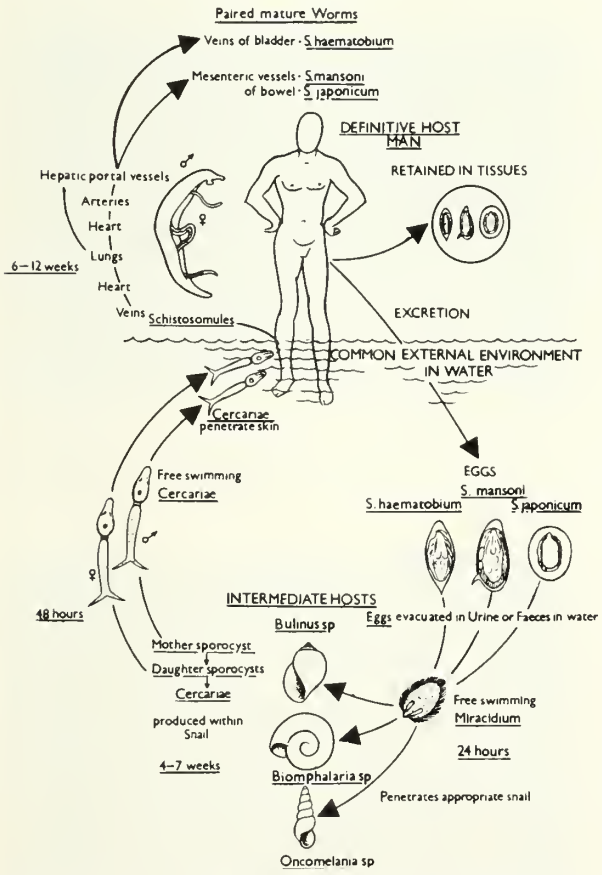

Figure 1.—Life cycle of schistosomes. (Reprinted with permission from the authors and publisher of Jordan P, Webbe G: Human Schistosomiasis. Springfield, IL, Charles C Thomas Publishing Co, 1969, p 7.)

Life Cycle and Transmission of Schistosomes

Egg Stage

Before considering newer realms of treatment and immunology, let us briefly review the transmission pathway (Figure 1). The parasite is spread via eggs passed into the water. The three species can be clearly differentiated by the characteristics of their eggs: the terminal spine of the bladder or vesicular schistosome, *Schistosoma haematobium;* the heavy lateral spine of the *S mansoni* egg is diagnostic, and the smaller, more rounded egg of *S japonicum* has a characteristically inconspicuous lateral spine. *S mekongi* eggs are essentially identical to those of *S japonicum.* The eggs of all four hatch immediately upon immersion in the water, releasing a fully developed ciliated *miracidium* that swims rapidly and seeks to penetrate its particular host species of freshwater snail. Each schistosome species can develop only in its own snail host. If it succeeds in entering the wrong species it will be rapidly encapsulated and killed.

Larval Stages

Following penetration of the appropriate snail, a vast multiplication of distinctive larval forms occurs. In a few weeks the larval stage infective to humans, the cercaria (indistinguishable among the four species), leaves the snail and swims with a rapid oscillation of its elongated forked tail, seeking the skin of a human host. Each day at approximately the same time, hundreds of the thrashing cercariae swim from the snail, and rise to hang from the water surface. When the presence of human skin is sensed, possibly by skin oils and carbon dioxide, the cercariae respond instantly and swim towards it. They attach and, in a few minutes to half a hour, they penetrate, aided by hydrolytic materials from the parasite and by surface tension of drying droplets of water on the human host's skin surface. The cercaria then drops its tail as it penetrates and enters the human circulation. The young worm rapidly un-

dergoes profound morphological and physiological changes to become a schistosomulum—the preadult migratory schistosome, which in about a week migrates to the liver. There, growth, development of the reproductive systems, maturation, and mating occur in about six to eight weeks.

Paired mated worms (the male enclosing the far more slender female in its copulatory canal) then migrate from the hepatic portals into the mesenteric veins *(S mansoni* and *S japonicum),* or into the vesicular plexuses and veins *(S haematobium)* (Figure 2). Eggs are laid by the hairlike female worm, beautifully adapted to leave the semipermanent copulatory embrace of her mate and crawl up into capillaries deep in the intestinal submucosa or even into the villi. There she lays a few eggs, then moves into another capillary, probably laying 300 or so eggs a day (3,000, often in large clusters, in the case of each *S japonicum* female). Initially, these eggs work their way through the capillary wall. Each egg is aided by histolytic secretions from the miracidium which works while the lateral or terminal spine on the shell anchors the egg in the blood vessel until it can slip through the few intervening mucosal cells and into the intestinal or bladder lumen. The eggs now need only pass to the outside in feces or urine and hatch immediately on contact with fresh water. Each hatched egg releases its ciliated miracidium, the snail-seeking larva within, and the cycle repeats—though the larva must locate its proper snail host within two to three hours to survive. If successful—the one in several million—it penetrates the snail and begins again its extraordinary process of larval multiplication.

Human Host Response

Eventually, the infected human responds to the presence of schistosome eggs in its tissues, resulting in an inflammatory reaction. Ultimately, many of the eggs—perhaps 50 percent to 60 percent—are caught in the ensuing granulomatous host response (Figure 3). Apparently, the lytic products secreted or excreted by the miracidium within the eggshell are highly immunogenic, inducing the granulomatous response that captures and encloses the egg. The disease that we know as schistosomiasis is, as noted, a host over-response to miracidial immunogenic substances, resulting eventually in thickened, fibrosed tissues that impede normal peristalsis or bladder function. A great range of pathological changes result, varying with the degree of host response and the location of the eggs.[7] Some eggs fail to work their way into the tissues or gut lumen and are retained within the blood vessels. These eggs are carried with the blood flow, via the mesenteric vessels into the liver portals. There new damage results, varying from small localized granulomata on liver or spleen surface, to deep tissue reactions, to massive portal fibrosis, causing hepatomegaly, portal hypertension, esophageal varices, ascites and hematemesis. Intestinal polyposis, as well as thickened walls, may occur with *S mansoni.* Hydroureter and hydronephrosis accompany *S haematobium* infection; even a few eggs in a critical location can block or slow urine passage into the bladder. Eggs may be shunted past the liver and be lodged anywhere in the body, including egg patches in the skin. A common site of extrahepatic egg deposition by *S mansoni* is in the lung arterioles; deposition here is frequently followed by fibrosis, and, in extreme cases, by cor pulmonale. Myelopathies and brain damage have often been reported, especially with *S japonicum.* But most of the eggs held

Figure 2.—Histopathologic section of a male schistosome worm enveloping a female worm in his copulatory canal. (Reprinted with permission from H. Zaiman, MD.)

Figure 3.—Eggs of *Schistosoma mansoni* surrounded by a granulomatous reaction.

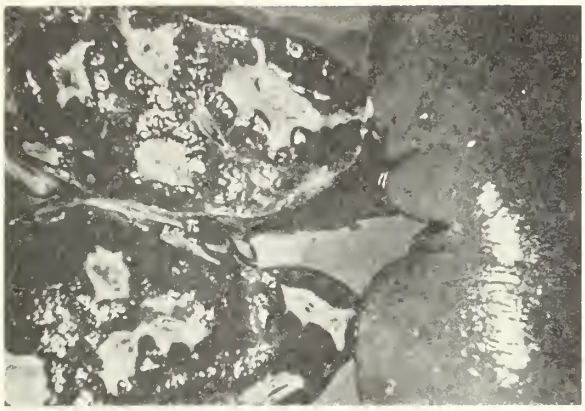

Figure 4.—A cross-section cut of a liver showing Symmer clay pipe-stem fibrosis. The white color is caused by the massive fibrosis enclosing the portals.

in tissues are trapped by the millions in gut or bladder walls, resulting in tissue thickening, disruption, and loss of normal function.

Napoleon called Egypt the land of male menstruation. Among the early discoveries by the remarkable medical contingent that accompanied his Egyptian invasion force was the bloody urine so frequently passed by Egyptians, especially young males. These are the early stages of *S haematobium* pathogenesis—rupture of vesicular blood vessels. Inflammatory cell infiltration of the bladder wall follows, a giant cell reaction producing a full granulomatous response. Pseudotubercules are formed, each enclosing a schistosome egg (positive for periodic acid Schiff stain) in the center of the granuloma. An extreme example of fibrotic damage to the liver, most frequently associated with *S mansoni,* is a condition called Symmer clay pipe-stem fibrosis, seen in liver sections when the portal is cut in cross-section (stem of the pipe), the white color being caused by the massive fibrosis enclosing the portals (Figure 4).[7]

Schistosomiasis in the United States

A very different form of infection occurs in the United States, where human-infecting worms are absent, but where other schistosomes are commonly found in aquatic birds. Cercariae from infected snails may penetrate human skin, but cannot survive long there and do not migrate into the liver for further development. They are adapted to their normal bird environment, or, in other cases, to an aquatic mammal, such as the muskrat. The result is that the worms are not able to respond normally in the strange human milieu and, thus, are trapped and killed in the skin by a nonspecific response to a foreign body. A sensitization process ensues after the worms are killed, and the next time cercariae are trapped in the skin a rapid inflammation occurs. This causes an allergic and painful or extremely pruritic swimmer's itch or cercarial dermatitis, reported from both freshwater, estuarine and marine environments in the United States and other temperate regions—wherever migratory aquatic birds, such as ducks and geese, collect. Many camp and summer resorts have been economically ruined by the presence of snails that serve as hosts for these avian parasites. Control depends upon destruction of the host snails—an often difficult, costly and long-term process, with environmental or ecological damage to other aquatic organisms an added threat.

Schistosomiasis in North Africa and Egypt

In North Africa and Egypt, carcinoma, both squamous cell and adenocarcinoma, is common along with the vesicular fibrosis caused by *S haematobium*. There is probably more bladder cancer in Egypt, coinciding with areas of heavy *S haematobium* infection, than anywhere else in the world. There still is no proof of direct causation, but the correlation is undeniable. Fortunately, these extreme cases are relatively rare in a land where 40 percent to 60 percent of the people are infected, but nonetheless they are of significance. The duration and frequency of early exposure is apparently critical in determining the size of the infective worm load and probability of future pathology. In a tourist or traveler with a brief exposure (but with a fully matured immunological system) a very different infection will develop from that in a child whose exposure began at a very early age, perhaps as an infant being washed in a stream or irrigation ditch near a concentration of infected snails. For these infants it is possible that a condition akin to immunological tolerance develops, delaying for some years the pathological hypersensitization response that results in tissue damage. Schistosomiasis, in other words, is not a disease caused by a parasitic worm in the sense of a toxic infection, but a disease caused by a worm *and* the host response.

Drug Therapy

Drug therapy is available, though until very recently the therapeutic regimen was difficult, lengthy, costly and toxic. Trivalent antimony was about all we had. Antimony potassium tartrate,

or tarter emetic, an extremely toxic trivalent antimony drug, given intravenously as a 0.5 percent solution in a 15- to 30-day course has for years been the only really effective drug available against *Schistosoma japonicum,* the most pathogenic schistosome. Stibocaptate, an antimony sodium dimercaptosuccinate, was available for the other two schistosome species, given intramuscularly in a 10 percent solution weekly for five weeks. Stibophen—which was given the trade name Fuadin after Fuad, the first king of modern Egypt—was another toxic drug given intramuscularly over one or several courses of two to three weeks. All of these usually produced nausea, vomiting and pain at the site of injection. Neuropathy was common and other untoward symptoms made the drug unusable for mass therapy and difficult to use even in hospitals.

Hycanthone, also given intramuscularly, was a treatment breakthrough, being a single-dose drug. It had been difficult to hold people in the hospital for a 17-day drug course, although stibocaptate had been used on a large scale in Africa as a *suppressive* drug, given intravenously in a dosage of 8 to 10 mg per kg of body weight once a month for about six months. So the obvious advantage of a single injection was overwhelming. Some 500,000 doses of hycanthone were successfully delivered in South America and Africa, until further testing indicated the ever-present triple threat of mutagenicity, teratogenicity and carcinogenicity. Though hundreds of thousands of cases had apparently been successfully cured in endemic areas, the long-term effects based on animal studies and Ames test results caused hycanthone to be taken off the market. We had only niridazole (Ambilhar) left, a nitrothiazole compound, until recently the only acceptable oral drug for use in this country against imported cases.[9] It is given orally but still can be toxic, requires a five- to ten-day daily course, and is often unsuccessful.

Single-Purpose Schistosomicidal Drugs

A welcome development in recent years, therefore, has been the discovery and testing of single-purpose schistosomicidal drugs. Metrifonate (Bilarcil), an organophosphate, was found to be effective against *Schistosoma haematobium* when taken in three oral doses (every other week). It is currently accepted for experimental clinical use in the United States, but it is effective only against the bladder fluke. The drug is available for this purpose from the Center for Disease Control (CDC) in Atlanta. Metrifonate is of a very low order of toxicity, is refreshingly inexpensive, and remains unblemished so far from charges of mutagenicity or other undesirable effects—other than requiring three doses at two-week intervals. This drug also has prophylactic power when given at four-week intervals in endemic areas, giving it a high potential for treatment of tourists, though this use of the drug has not yet received Federal Drug Administration clearance. Similarly, a synthetic derivative of hycanthone, oxamniquine (Mansil), is now available against *S mansoni.* It is also given orally and is a single-dose drug for the American *S mansoni* strain. However, it is given twice, at twice the dosage if the disease is acquired in Africa. This is still a distinct advantage over three doses at two-week intervals, though, unfortunately, at a cost ten times higher than metrifonate. Oxamniquine is also of a low order of toxicity. Though not yet approved for experimental use through the Center for Disease Control, clearance is expected within a few months. These two drugs are a dramatic improvement in the armamentarium against the two commonest schistosomes of Africa.

Schistosoma japonicum, however, cannot be touched by either metrifonate or oxamniquine. Another exciting new drug, praziquantel, an isoquinoline pyrazine, may be the answer.[10,11] It is currently being tested as a multipurpose drug, effective against all three common human schistosomes and, for good measure, any *tapeworms* one happens to harbor. It is effective both orally and intramuscularly, appears to be nontoxic, and is clearly the most promising new anthelmintic drug on the horizon. For *S haematobium,* 200 mg per kg of body weight in one dose has been tried. Against *S mansoni,* three doses of 50 mg per kg of body weight given in one day seems to work. For *S japonicum,* an oral dose of 100 mg per kg of body weight for three days is being experimentally studied.[11]

Dosages tested vary considerably in different parts of the world, but effective mass treatment of schistosomes is now far nearer than it has ever been, made possible by these oral drugs, which require only a small number of treatments, have low toxicity and promise a rapid cure. But mass therapy is still a long way off, pending further drug testing, cost reduction and sociopolitical acceptance. Drug reversal of tissue damage also seems to be the rule in most cases. In one case reported, a large lesion from an ectopic concen-

tration of schistosome eggs in the spinal column caused a myelopathy that turned the patient into a quadriplegic. He was treated with niridazole, the egg-induced granuloma receded and finally disappeared, and the patient returned to full normal ambulatory behavior.[12] Similarly, inflammatory changes, obstructive uropathy, polyposis, and even liver damage disappear with timely treatment. If large-scale drug use brings the price down substantially, we have, for the first time, a means to make real progress on what is still the fastest spreading and most dangerous helminth of mankind.

Future Prospects for Successful Treatment

Prospects of an effective vaccine or of a specific, sensitive, simple and inexpensive serodiagnostic procedure are far less sanguine. This is due in part to the strong immunogenicity of the worms or of their secretory-excretory products (especially the soluble antigen passed through the eggshell from the miracidium).[1] Numerous antigenic stimuli are clearly present as circulating antigens and as antigen-antibody complexes. But this very variety and complexity of antigens makes the selection, isolation, and large-scale production of the appropriate one for diagnosis, or a *functionally* protective antigen an extremely difficult task. There is an immediate and a delayed hypersensitivity from which a variety of relatively nonspecific skin tests have been developed. Considerable progress has been made in developing a purified antigen able to separate the species, with possible adaptation to field use. However, a screening serodiagnostic test usable on a large scale is still a relatively distant goal.

Other Serodiagnostic Procedures

Other forms of serodiagnosis are available for use in sophisticated diagnostic laboratories. In this country that is almost entirely the responsibility of the General Parasitology Branch of the CDC, which will carry out such tests free of charge if the serum sample is sent via the State Public Health Laboratory with an appropriate patient history. The most accurate test now in use depends on a circumoval precipitin reaction. This is an in vitro precipitation test around schistosome eggs. It will indicate the species involved as well as the general reaction. Another test, the cercarienhüllenreaktion, is a precipitation around the cercaria, another quite specific response. Other serodiagnostic procedures have been evaluated or are under development: complement fixation, indirect immunofluorescent antibody, indirect hemagglutination, bentonite flocculation, cholesterollecithin flocculation, immunodiffusion, immunoelectrophoresis, ELISA (enzyme-linked immunosorbent antibody test) and countercurrent electrophoresis.[13,14] This battery of tests gives us a new serodiagnostic potential, especially the indirect hemagglutination and indirect immunofluorescence tests. But it is only the beginning.

Experimental Immunology

The most interesting work, and the most active and intriguing area of schistosome research, is experimental immunology, with the ultimate—and by no means reached—objective of a protective vaccine. A discovery made about ten years ago, concomitant immunity, was briefly alluded to earlier. It has been found that a concurrent infection protects the host against an incoming *new* infection—so long as the old one remains alive to initiate a host antibody and cell immune response. Somehow, that response is ineffective against the standing infection. The original invading worms, after their migration to the host liver, appear able to collect or elicit formation of a coating of host material onto their own tegument, thereby disguising their presence within the host, changing from host nonself to self.[15] Any invading larvae that can reach the liver before the host can build up its antibody levels and initiate an immediate hypersensitization response, will probably survive. These first invaders, coated with host substance, can then make their way into the mesenteric vessels and may survive there for 25 years or even longer. The *next* batch of schistosomula to invade, however, may encounter an antibody-initiated hypersensitivity response, with an additional cell-mediated immune reaction, before the worms can acquire their protective coating. They are usually killed in the skin within 48 hours. A modification of the host T cell response and its immunoregulation also appears to develop, observed as T cell suppression or modification of lymphocyte deoxyribonucleic acid (DNA) synthesis. Worm antigen not only can elicit a host pathogenic response, but can depress the T cell reaction as well, inhibiting the hypersensitivity response. If a T cell cancelling drug is given to experimental mice, the granuloma around the cell is sharply reduced—but the hosts die more rapidly. An interesting balance evidently occurs. With nude, irradiated or immunosuppressed mice, no granu-

loma is produced, but more rapid death ensues; with a strong granulomatous response, illness develops, but host survival is extended. This oscillation between reaction and over-reaction governs the host-parasite balance, ranging from massive parasitism to massive response and tissue destruction.

As far as induced immunity, another spectrum of responses can be seen. Rhesus monkeys exposed to irradiated cercariae develop a protective immunity. But this does not occur with chimpanzees, which are far more humanlike in their response. Rats and rabbits are naturally resistant and do not need such a stimulus. In Taiwan there is an animal strain of *S japonicum* that cannot infect humans, but does infect cattle, dogs or other animals. We can immunize monkeys with this strain, but cannot yet risk human experimentation. Cross-immunity therefore is an unproved but possible approach to human protection.

Role of the Eosinophil

The role of the eosinophil is the most recent and spectacular breakthrough in schistosomiasis research. This heretofore mysterious cell appears to be a complement-dependent killer cell of schistosomes and other invasive parasites. It adheres to the tegument of the worm and actively breaks down the target worm's exterior surface during the cell's degranulation.[1-4] Death of the schistosomula generally occurs in the skin but must take place within the seven-day period of migration to the lungs and to the liver. After that the worm is quickly protected by its host's antigenic coating. After eosinophil degranulation, lymphokines appear, then a monocyte and a lymphocyte reaction; and finally a T cell response occurs, somehow modified by the worm's own antigens. Some of the invaders may still be able to reach the liver in spite of this protective response, add a protective overcoat, develop, migrate into the mesenteric vessels, and join the original population of blood flukes. This host-parasite complex of invasion, response and counterresponse illustrates well the complexity of this host-parasite interaction. No longer can we think simplistically of "catching" an invasive organism, whether microbe or worm. Now we must also evaluate the host reaction, from tolerance to immunity to hypersensitization to autoimmune illness. Schistosomiasis is one of the best tools we have to help delineate this extraordinary interaction process.

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Important Advances in Clinical Medicine

Epitomes of Progress—Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in plastic surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Argon Laser Treatment of Cutaneous Vascular Lesions

ARGON PHOTOCOAGULATING LASERS have proved to be very useful in the treatment of port-wine stains (nevus flammeus) and other superficial cutaneous vascular anomalies. Highly focusable blue-green laser light is selectively absorbed by the red color in capillaries in skin and mucous membranes where it is transformed into heat intense enough to cauterize small vessels up to 0.5 mm in diameter. Other skin structures such as hair follicles and sweat glands are relatively spared, allowing reconstitution of the epidermis with minimal or no scarring in many patients. Histopathologic studies show changes of collagen coagulation in the upper 1 mm of the dermis, with an associated pronounced increase in collagen deposition and destruction of small vessels in the treated areas; the resultant wound is similar to a superficial second degree burn. Biopsy specimens taken three years following treatment showed dense fibrosis in the upper dermis, as well as no evidence of nuclear mutation or any indication of malignant degeneration.

More than 300 port-wine stains have been treated with argon photocoagulating lasers. Good results, with substantial lightening in color, have been obtained in 65 percent to 70 percent of patients. Excellent results, with complete eradication of the lesion, are uncommon. An associated benefit of laser treatment is the ablation of nodules or a flattening of the cobblestone texture of the involved skin often seen in patients over the age of 35 years. Scarring, the most undesirable complication, is seen in approximately 5 percent to 7 percent of patients; the perioral area is most vulnerable to this particular complication. In 20 percent to 25 percent of patients treated there was little or no improvement. The laser appears to have the most salutary effects on lesions of the face and neck; treatment of trunk and extremity lesions has been disappointing. It may take many months to treat completely a large port-wine hemangioma extending over major areas of the face or neck. Patients are treated under local anesthesia as outpatients, or in some instances in an operating room under general anesthesia.

Telangiectasias, pyogenic granulomas and small capillary angiomas respond well to the blue-green laser light. Bulkier lesions such as cavernous hemangiomas do not respond well, if at all, to laser treatment. Decorative tattoos may be substantially lightened when exposed to an argon laser, but there always remains a "ghost," and scarring may be a prominent problem. Nevi and skin

cancers should not be treated with the argon laser.

Argon laser treatment facilities exist throughout the United States. Plastic surgeons and dermatologists interested in using the laser for the treatment of cutaneous lesions have attended regional symposia sponsored by major medical centers with laser facilities and by leading laser manufacturers.

Several major insurance carriers have elected to cover the cost of treatment of port-wine stains, but may not reimburse patients for the treatment of other cutaneous vascular abnormalities and tattoos.

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Topically Applied Antibacterial Agents for Burns

A MAJOR ADVANCE in burn care has been the introduction of topically applied antibacterial agents. Since the initial use of silver nitrate, it has been recognized that the use of topical agents serves to reduce the mortality from major burns. Silver nitrate is still used today in a 0.5 percent solution or else in the form of a cream. Most burn care centers have switched to mafenide acetate (Sulfamylon) or silver sulfadiazine (Silvadene). Neither of these agents should be used for minor burns. Both are extremely effective against a wide variety of organisms, and mafenide acetate has the ability to penetrate the thick burn eschar as well. Because of pain on application as well as associated metabolic and respiratory problems at the time of initial treatment of major burns, mafenide acetate has been supplanted by silver sulfadiazine—which is now the antibacterial agent most commonly used in this country for topical application to burns.

Two topically applied agents used less frequently are providone iodine (Betadine) and gentamicin sulfate (Garamycin). The use of providone iodine is controversial because multiple dressing changes are required each day to be effective, and there is little evidence of eschar penetration. Gentamicin sulfate was not designed for major burn injuries; it produces resistant *Pseudomonas* organisms very rapidly when applied to a large wound surface.

Topically applied antibacterial agents, used in combination with early wound excision and coverage by autograft skin or other biologic dressings, have greatly reduced the morbidity and mortality of burns, especially in the past decade. The key to the survival of patients with major burns is early skin coverage. Topically applied agents cannot be relied on to prevent sepsis indefinitely.

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The Intraoperative Use of Fluorescein as an Indicator of Tissue Viability

FLUORESCEIN IS A nontoxic dye that rapidly distributes itself in the extracellular space shortly after intravenous injection. It has been shown in a large number of cases to predict reliably the adequacy of the microcirculation. Proper interpretation of the test results is essential, and this can only be learned through experience.

Fluorescein was first used in 1882 by Paul Ehrlich. Lange and Boyd in 1942 used it to determine circulation times. Recently, it has been used by ophthalmologists for retinal angiography and by other surgeons to determine tissue viability. Myers first brought it to our attention as an accurate predictor of flap survival after mastectomy. McCraw and co-workers showed its reliability in 159 cutaneous flaps and 126 musculocutaneous flaps.

Fluorescein can safely be given intravenously in doses of 10 to 20 mg per kg of body weight. The incidence of allergic reactions has been reported as 0.6 percent in a large series of cases. Most of these were manifested by urticaria only. Occasional cases of anaphylaxis have been reported, with no known fatalities. Nausea and vomiting may occasionally occur if the drug is administered too rapidly in patients who are awake.

The drug is injected after all tissue dissection has been completed and the flaps are in place. A dose of 15 to 20 mg per kg of body weight is given intravenously over a two-minute period. It is usually necessary to double the dose in black patients for adequate visualization. This is quite safe: the LD_{50} (lethal dose for 50 percent survival of group) experimentally is 1,000 mg per kg of body weght.

After 15 to 20 minutes the dye is distributed

in the extracellular space, but only in those areas with intact microcirculation. It does not depend on or correlate with blood flow or intravascular concentration. To interpret the test results, the operating room must be darkened and a source of ultraviolet light, such as a strong Wood's lamp, must be directed on the area being investigated. Viable tissue fluoresces brightly with a yellow or chartreuse hue. Nonviable tissue appears as a solid purple mass. Areas that show spotty fluorescence are equivocal, but they usually survive—especially if there is a dense distribution of the spots.

Clinically, fluorescein has been used primarily with skin and musculocutaneous flaps. We now also use it to assess tissue viability in the primary debridement and grafting of all avulsion injuries. The skin from these areas, if not directly traumatized itself, can be successfully used as the donor source for meshed split-thickness skin grafts.

Fluorescein has been shown in laboratory studies to predict accurately the nonviable intestinal margins after mesenteric arterial occlusion. Clinical application of this use of the dye may potentially spare some patients second-look operations to determine bowel margin viability.

Fluorescein is now being studied as an aid in burn debridement to determine the depth of burn injury accurately. This may also be applied to electrical burns, where the zone of necrosis may be harder to determine and is often deeper than first suspected.

Another clinical use of fluorescein now being studied is in determining amputation levels in patients with peripheral vascular disease, particularly with the small vessel disease of diabetes mellitus. It appears to be less helpful in debridement of areas of small vessel injury secondary to radiation therapy.

A unique use of fluorescein we have seen is in identifying the point of thoracic duct leak at the time of neck dissection. The yellow-green dye in the normally clear lymph immediately pinpointed the source. Similarly, a ureteral leak can be detected (although other dyes have been used nicely for this).

In summary, fluorescein is a safe, simple, rapid, reliable and reproducible method of determining tissue viability. Confidence in its interpretation and its usefulness develops with experience.

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Enzymes for Debridement

ENZYMATIC DEBRIDEMENT of wounds enjoyed a brief popularity when introduced a decade ago. These early agents—fibrinolysin and desoxyribonuclease (Elase)—reportedly affected necrotic tissue by fibrinolytic action, but the clinical results left much to be desired. More recently developed proteolytic agents have revived the use of wound debriding enzymes. Their effectiveness is based on breaking down collagen fibers which make up tenacious devitalized wound tissue—collagenase (Santyl)—or by fribrinolysis—sutilains ointment (Travase).

Debridement of a wound is preparation for healing. Surgical or enzymatic debridement can be elected, depending on the patient's individual circumstance. Ease of bedside or outpatient application make the enzymes an attractive alternative to the more complicated and expensive formal surgical operation. Further, both approaches may be used on the same patient, singly or simultaneously.

Enzymatic debridement with sutilains ointment is widely used in the treatment of burned patients, but it has also found application in treatment for pressure sores and leg ulcers. Best results are obtained when the agent is in a moist environment. A thin layer of ointment is applied directly to the necrotic wound surface, then covered with moistened gauze. An antibacterial solution may be used for moistening, excluding compounds that deactivate the enzymes (such as the iodophors). The entire dressing system is replaced every six to eight hours, removing the loose debris with each change. Proteolytic activity should be noted within 24 to 48 hours. If no appreciable beneficial changes occur in this period, the enzymes may be considered ineffective and an alternative plan instituted.

Local allergic reactions are infrequent and minor. The single specific contraindication is use in wounds grossly infected with pathogens. The enzymes tend to break down damaged tissue planes, enhancing local spread.

A dose of 30 grams of sutilains ointment usually

is sufficient to debride an ulcer 5 cm in diameter and 2 cm deep for three days. The cost of the enzyme ointment is approximately $10 for 30 grams.

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Dextranomer for Chronic Leg Ulcers

SKIN ULCERATION of the legs is one of the more difficult and persistent problems seen by physicians and endured by patients. Whether the cause is arterial ischemia, venous stasis or systemic collagen disease, the most effective methods of treatment are direct corrections of the underlying disease process. Once this has been attempted (whether successful or not) the basic principles of ulcer management consist of removing necrotic material, protecting and promoting healthy granulation tissue, and achieving either spontaneous or surgical closure.

The frequent appearance of new topical products for the treatment of skin ulceration attests to the lack of consistent effectiveness. The newest product to be promoted is dextranomer (Debrisan). It is a highly hydrophilic, large dextran polymer packaged as small dry beads measuring 0.1 to 0.3 mm in diameter. These beads are sterile and have the appearance of granulated sugar. The material is chemically inert and is believed to work by molecular and capillary absorption of fluid from the wound. This draws bacteria and wound breakdown products away from the surface. Heavily secreting or exudating wounds are more amenable to treatment by this method than are dry wounds. Experimentally, the bacterial concentration is said to be greater at the advancing fluid interface in a column of dextranomer beads than at the base of the column.

The initial anecdotal clinical experience with the product was very promising. There now have been two randomized controlled studies in the United States which have indicated that dextranomer can be used successfully in the treatment of moist wounds such as venous stasis ulcers. It is much less effective in arterial or vascular ischemic ulcers. Frank and co-workers compared dextranomer with saline dressings in reducing quantitative bacterial counts in open wounds. Moist saline dressings were used as a standard of comparison because they are inert and act by absorbing excess exudate, mechanically removing debris and preventing dehydration of granulation tissue. No superiority could be shown for dextranomer. Pain on application, due to dehydration, and progression of skin ulceration occurred in a few patients when the product was used.

For most patients a direct approach to removal of necrotic material from leg ulcers by enzymes, chemical agents or surgical excision appears preferable to the use of dextranomer. If cellulitis of the surrounding skin is present, this can be controlled with systemic administration of antibiotics and topical application of antibacterials such as silver sulfadiazine or mafenide. Once granulation tissue is developing it must be protected from dehydration and physical trauma. Many inert substances (such as saline, antacids, egg white, granulated sugar and dextranomer) have been used successfully.

As with many new treatment modalities, the initial appearance of success is due more to the interest of the investigator and the vigor of the nurse in applying the treatment than to the substance itself. Chronic leg ulcers remain an unsolved problem. After primary treatment is directed toward the underlying disease process, the use of dextranomer is an alternative method of treatment that will benefit some patients. This result may be due to the fact that the product is new and had not been used before in this particular case.

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Triamcinolone for Hypertrophic Scars and Keloids

HYPERTROPHIC SCARS and keloids represent opposite ends of the spectrum of undesirable healing. Hypertrophic scars, on the one hand, respond to surgical therapy and gradually resolve with time. Keloids, on the other hand, enlarge with time and surgical intervention often makes them worse.

Triamcinolone is a synthetic corticosteroid with a pronounced anti-inflammatory action. There are two commercial products available: triamcinolone diacetate (Aristocort) and triamcinolone ace-

tonide (Kenalog). The latter has a more prolonged action (up to four or five weeks). Both preparations persist in suspension at the site of injection.

Triamcinolone has a potent local atrophic effect which can be exploited in the treatment of hypertrophic scars and keloids. Unfortunately, there have been no controlled studies that clearly define the genuine value of this drug. The experience of many physicians, however, provides ample anecdotal evidence of its efficacy.

Most writers recommend a triamcinolone acetonide suspension (Kenalog-40) containing 40 mg per ml of the corticosteroid, despite the proscription of the drug insert that states "NOT FOR INTRADERMAL USE." (The manufacturer, E. R. Squibb & Sons, Inc., advises that this recommendation results from a lack of test data rather than any reported harmful effects. Squibb emphasizes that intradermal injection of nonhypertrophic lesions does provide risk of local atrophy). The suspension should be injected directly into the scar and never into the surrounding cutaneous fat. A pressure jet apparatus may be used but the depth of penetration in a tense, rigid scar is uncertain. Injection may be preceded by local infiltration of lidocaine (Xylocaine) or else the suspension may be mixed with local anesthetic before administration. The maximum dosage is 60 mg (1.5 ml) every 30 days. Considerable injection force is required. Initial treatment of an active scar may leave one with the impression that little or no drug actually entered the scar. Repetitive injections will be required to distribute the drug throughout the lesion. A satisfactory response is characterized by softening and decreased itch and burning. Subsequent injections will require far less force to achieve satisfactory drug dispersal. Maximum dose limitations restrict the use to relatively small lesions. Large plaques of scar are impractical to treat by injection of the product.

Several treatment schedules have been recommended:

- Small lesions are injected at a sufficient number of sites to assure adequate distribution. This is repeated at one- to two-month intervals until the desired degree of scar involution is obtained (usually three to six treatments). If hypertrophy recurs, several courses may be required. If there is no improvement after three injections, treatment should probably be abandoned.
- Larger lesions or those with epithelial sinuses, cysts, or the like, can be excised. Wound closure should be with a subcuticular, nonreactive, removable suture. Skin sutures are to be avoided. Triamcinolone may be injected into the wound edges at the time of surgical therapy or delayed until the first signs of hypertrophy occur. True keloids may return in larger proportion despite all treatment efforts.

Scar atrophy is evidenced by flattening, but not narrowing, of the scar. The epithelium will appear thin with telangectasia and occasionally with permanent whitish flecks of residual drug. The symptoms of itching and burning should lessen dramatically.

Radiotherapy for keloid and hypertrophic scars is to be discouraged, especially in children. It simply does not work and leaves the patient with a lifetime of local radiation effect.

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Acetylsalicylic Acid's Effect on Surgical Procedures

In 1943 Rudolf Singer noted a decrease in both bleeding and palatal bruising after tonsillectomy if acetylsalicylic acid (aspirin) was avoided. In 1964 the results of a double-blind study confirmed this observation, showing that acetaminophen (Tylenol) was better than aspirin in relieving pain and fever, and that it did not cause bleeding.

It has now been determined that one standard dose of acetylsalicylic acid will acetylate protein in the membrane of all platelets in existence at the time the dose is taken. The effect lasts the life of the platelet, ten days, and interferes with the ability to aggregate and to secrete ingredients important to the coagulation process.

The most easily detectable effect is prolongation of bleeding time. Large amounts of exogenous thrombin or collagen will tend to reduce the bleeding caused by aspirin damage to platelets. The aspirin effect on coagulation is now so well accepted that aspirin is used in the management of cardiovascular states where inhibition of clotting is beneficial.

Certainly, with this information, patients should be advised to avoid aspirin for a least a week before a reconstructive surgical procedure. Aspirin

damage to platelets does not affect the platelet count.

Since excessive bleeding interferes with carrying out surgical procedures, and hematomas adversely affect the results, elective procedures should be avoided while platelets are crippled by recent aspirin ingestion. When an emergency surgical operation is necessary in the presence of the aspirin effect, platelet transfusions are useful.

A normal finding from a correctly done determination of bleeding time indicates the absence of significant aspirin effect. Confusion is frequent because more than 100 proprietary drugs in the United States contain acetylsalicylic acid.

It should be emphasized to patients that they must not take aspirin in the ten days preceding an elective operation.

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EDITORIALS

Significant Others in Patient Care

SOMETHING SORT OF SCARY has been happening in patient care. The close and mutually satisfying relationship between physicians and patients still exists, but one can sense that this hitherto hallowed relationship seems to be losing ground, both quantitatively and qualitatively. Somehow it seems not to be fitting the times as well as it did. One wonders whether this is because physicians are changing, or because other changes are coming about in this field which has been largely the province of physicians who wanted to take care of patients and of patients who sought or needed the care of physicians. It is always a little unnerving when something that has been widely accepted as a given, or an article of faith, appears to lose general, unquestioned acceptance. Yet more and more physicians and more and more patients seem to be seeking alternatives to the stereotype of the trusted physician and the cooperative or compliant patient.

Some of what has been occurring is explained easily enough. It has to do with scientific progress and social change. The remarkable progress in medical science and technology during the last half century has caused many physicians to become so specialized that in reality they are superbly skilled technicians. This has been at the expense of interest, or even experience, in the broader aspects of patient care. Patients on the other hand are developing greater sophistication (or perhaps pseudosophistication) about medicine and health care, and are playing a more active role in decisions about their medical care and in determining where they will seek it and from whom they will accept it. All this has led to a curious deprofessionalization of the health professions, while at the same time many kinds of workers in the health field are either seeking professional status or trying to enhance what they have. This latter applies to nurses, pharmacists, podiatrists and optometrists, for example, while a number of technician specialties are gradually achieving recognition as professions. Then the egalitarian thrust in today's society tends to have a leveling effect across the board. And along with this there has been greater public and patient acceptance of methods and approaches to health care that physicians consider to be unscientific, unproved or even dangerous.

Therefore, it seems obvious that there are now significant others who are becoming increasingly involved in patient care, and that these are many. The pressures for independent practice by health professionals other than physicians are growing, as is the concept of equal pay for the same services regardless of the extent of training or qualifications of those who render the services. In another dimension, practitioners of chiropractic have now attained licensure in every state, and reimbursement for their services has been authorized by Medicare, Medicaid and many private insurance carriers. Such trends, of which these are examples, suggest that in the foreseeable future patient care may become considerably less structured or perhaps even something of a free-for-all. These problems may be made simpler or more complex by the surfeit or excess of physicians which is expected in the next decade or so.

While medicine is still clearly the recognized leader among all the health professions, it is no

longer safe to assume that this will always be so. It is time for the medical profession to look at its role of leadership and to strengthen it. Our leaders spend a great deal of time and energy—and our dollars—defending the ramparts. While this is surely necessary, it likely will not be enough. The medical profession has strong roots in medical science and in the art of understanding and working with people, and helping them to cope in a caring way. The skills that medicine brings to patient care should now be used to affirm and strengthen leadership in all of health care. The medical profession—whether in practice, academia or wherever—should hoist the flag of leadership in health care, and organized medicine should become a crucible in which the future of patient care is hammered out and shaped. The role should be one of sure and effective leadership, working closely and collaboratively with all the significant others in health care, whether health professionals or not.

—MSMW

Thyroid Nodules and Thyroid Cancer: Other Aspects

In reviewing the surgical aspects of thyroid nodules and thyroid cancer elsewhere in this issue, Dr. Orlo Clark has presented documentation for widely held approaches to the problems faced by surgical specialists. The statistics cited by Dr. Clark define to some extent the problems that those of us who hold other notions encounter in giving advice to patients with thyroid nodules and possible thyroid cancer.

In our population of more than 220 million, a 4 percent incidence of thyroid nodules means that about 8.8 million persons will have need for medical advice about this condition. The statistic that 0.004 percent of the population will have thyroid cancer, if accepted without question, means that 8,800 persons will have the liabilities of this disease. Because in most of the 8.8 million persons the disease will develop over a long time, each of these persons could be the basis for many medical decisions on the significance of thyroid nodules.

I find it hard to accept that 10 percent to 15 percent of thyroid cancer is anaplastic, although few would dispute Dr. Clark's position that surgical removal is done for diagnosis, not for cure. If about one in eight persons with thyroid cancer had anaplastic cancer, then these 1,100 unfortunate persons would contribute almost half of the annual deaths, estimated at 1,150 in the United States, or 0.4 percent of all cancer deaths. Unless I have seen a very unusual population, that figure is much too high. An important consequence of this consideration is that other forms of thyroid cancer, including papillary cancer, do contribute a larger percentage of the total deaths from the disease than his figures indicate.

The problems of papillary cancer as a radiation-induced disease are introduced by Dr. Clark, but are not fully defined, probably in keeping with his restriction of content to surgical aspects. The induction of papillary cancer by radiation therapy has been much publicized recently, more than 25 years after the association was first recognized. Modan's figure of 6.5 rads for induction of thyroid cancer[1] is indeed frightening when viewed in the light of Table 2 in Dr. Clark's paper. Dr. Clark chose not to comment on the common practice of using iodine 131 scans in instances in which iodine 123 or technetium 99m scans provide inferior delineation. I continue to believe that the use of carcinogenic doses of radiation in diagnostic studies should be debated, as I first did with little success in 1957.[2]

The magnitude of the problem of induction of thyroid papillary cancer by radiation is unknown. Hundreds of thousands, quite possibly millions, of persons may have had their thyroid glands exposed to radiation dosages now known to carry the potential of cancer induction. Some investigators advocate adding this group of irradiated patients to those to be evaluated for thyroid nodules by the method recommended in Figure 1 in Dr. Clark's article, with total thyroidectomy to follow for those having even microscopic papillary cancer foci. The cost of such a program needs careful evaluation and must be measured in economic terms, morbidity and mortality. The benefit in the long run for each person is best measured by considering the average age at which death occurs from this disease; such data, although hard to come by, are very valuable in contrast to the rather inconsequential figures on survival after diagnosis. Clearly, unless harm is done by the treatment, earlier diagnosis will regularly be followed by more prolonged survival. More advanced age at time of death is a clear benefit.

Dr. Clark has provided a service in clearly stat-

ing that thyroid hormone administration is beneficial to patients with thyroid cancer by suppression of thyrotropin and its stimulatory effect on the cancer. His, I believe, is one of the first surgical articles to recognize this fact. The fact, however, is implicit in the practice of inducing hypothyroidism in order to stimulate the tumor to accumulate radioactive iodine. With this important recognition it may be time to call for some well-planned studies to learn what will benefit patients the most. For example, a collaborative study of a large group of patients is needed to test possible benefits of thyroid hormone prophylaxis of cancer, as compared with groups treated in more conventional ways, such as outlined by Dr. Clark. A call should go out for research funds to study means of predicting the biological behavior of thyroid tumors.

Some 33 years ago I wrote a brief article noting that although the incidence of diagnosed thyroid cancer was as high as 30 percent in thyroid nodules, thyroid cancer was a relatively rare cause of death.[3] The estimate of 1,150 deaths from thyroid cancer for 1976 speaks to this point. In the years since 1947, I have carried my full burden in trying to make death a little easier for patients with thyroid cancer—one with anaplastic cancer, another with a long-standing "simple goiter" that metastasized to lung and bone, and several with papillary and alveolar carcinoma. The earliest death was at age 52, the others occurred between ages 75 and 85. I also cared for patients with thyroid cancer burdened with bilateral vocal cord paralysis, severed spinal accessory nerve (unrecognized shoulder paralysis) or persistent facial edema after neck dissection, and a substantial number of permanently hypoparathyroid patients. During all of this, I was seeing referred patients in an institution that had no surgical services.

From these experiences, I must conclude that Dr. Clark has presented his case well. At the same time, I feel that greater selectivity must go into determining appropriate treatment for the many patients with thyroid nodules and for those with histories of irradiation. Having advised a substantial number of patients conservatively over many years, while my hair has grown white ("Patients," I used to say, "don't consult me to spare my hair from turning grey"), I am able to record that this far into my career I have had no one return to say that he or she wished I had advised a more aggressive approach. I shall continue to rely mainly on increased growth despite administration of thyroid hormone, as the primary criterion of danger in thyroid nodules.

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Accountability for Performance

SANAZARO'S SPECIAL ARTICLE which appears elsewhere in this issue foreshadows a new era of physician accountability for professional performance in patient care. In days gone by, when there was more caring than curing in medical practice and the precept was to do no harm, it was sufficient for a physician to be accountable to his or her own conscience. The risks and benefits of medical interventions were relatively small, except perhaps in surgery. The risks were accepted by patients as a matter of course and the benefits when they occurred were greatly appreciated. But this was before medicine became more scientific and began to develop measurable data usable in day-to-day patient care. As this latter has occurred patient care has moved much more into the scientific and also the public domain, and professional accountability for practicing physicians has taken on new dimensions.

Perhaps because both risks and benefits can be dramatic in surgery, the earlier efforts at accountability for professional performance must be credited to surgeons, who limited privileges in operating rooms to match performance capability and monitored results through tissue committees and morbidity and mortality outcomes. But in recent years the risks and benefits in nonsurgical or medical patient care have become much greater because medical science and medical technology know more and can do more, with greater benefit though often at greater risk. So it is now becoming necessary to develop better accountability for all aspects of patient care, whether medical or surgical.

As medicine itself becomes more scientific, patient care becomes more scientific; or, to put it

another way, as medicine becomes more scientific a more scientific approach to medical practice will be needed. In his paper, Sanazaro suggests three important points which are linked. The data base for a physician's practice performance is to be found in the patient care record, whether in office or hospital. Professional accountability, like fiscal accountability, depends upon adequate data and adequate records which can be reviewed and studied. Another point is that comparisons of practice data, whether among physicians, hospitals or regions may emerge as useful indicators of performance. And then he suggests (as he did at a recent California Medical Association conference) that some system of "performance assessment credits" be established to recognize and reward physicians who develop and study their own practice data and participate in objective measurement of their personal practice performance.

The idea of accountability for professional performance is one whose time has about come. It should be welcomed by all physicians in the interest of more scientific, more accountable and therefore better patient care.

—MSMW

Myocardial Perfusion Scintigraphy

Elsewhere in this issue, Dr. James McKillop presents an in-depth analysis of the history, technique and clinical applications of myocardial perfusion scintigraphy. As Dr. McKillop notes, perfusion scintigraphy using thallium 201 has been widely investigated and applied to the evaluation of clinical problems. When the main clinical question involves the diagnosis of coronary disease, stress perfusion scintigraphy followed by redistribution imaging has been shown by numerous studies to be more sensitive than stress electrocardiography, and probably more specific as well.[1] Although redistribution examination may lead to an overdiagnosis of infarction, this method presents a definite advantage over rest imaging in saving time and expense, and in reducing patients' exposure to radiation. If it is critical to establish the presence and extent of previous infarction in a patient without a history of such an event, but for whom abnormal results on redistribution imaging persist, a later rest image may be carried out for clarification.

Although stress perfusion scintigraphy frequently underestimates the degree of vascular involvement, it appears to be sensitive for the diagnosis of coronary disease in patients with triple-vessel involvement. It also complements stress electrocardiograms for identifying the high-risk lesions of triple-vessel and left main coronary artery disease.[2] However, it is important not to confuse the extent of coronary disease with the extent of stress-induced ischemia. While coronary angiography provides an anatomic measure of the extent of coronary vascular involvement, perfusion scintigraphy provides a physiological marker for the extent of ischemia and infarction.

Perfusion scintigraphy is a relative technique, providing a regional indication of blood flow in various areas of the myocardium, and does not provide an absolute marker of perfusion. There is no reason to believe that in patients with multiple-vessel coronary disease, stress-induced ischemia will develop in all myocardial regions at risk. More likely, ischemia will be manifest in the most underperfused region depending on the degree of narrowing of the supplying coronary vessel, modified by the effects of collateral perfusion and the level of stress achieved. These factors likely explain some of the discrepancies between the physiological findings on perfusion scintigraphy and the anatomic findings on angiography. Similarly, stress perfusion scintigraphy carried out in patients following coronary artery bypass graft operations does not simply reflect the state of graft patency, but the combination of graft status, the state of the native vasculature and the contribution of collaterals.[3]

As a noninvasive indicator of myocardial perfusion, thallium 201 scintigraphy provides clinicians with a unique tool to assess and monitor the pathological effect of anatomic coronary stenoses or other factors which may prejudice myocardial perfusion. It is not surprising, then, that transient coronary spasm may produce scintigraphic abnormalities. Likewise, in the hypertrophied myocardium of patients with tight aortic stenosis, ischemia can also develop in the presence of stress. Under these conditions a patient may have positive ECG and scintigraphic changes in the absence of narrowing of coronary vessels. However, such scintigraphic abnormalities should not be classified as false-positive results; they are likely related to true ischemic manifestations in the absence of coronary artery disease. A recent study[4] and several cases in our own experience

have documented localized stress-induced scintigraphic abnormalities in the setting of stress-induced ST segment elevation and transmural myocardial ischemia.

The physiological nature of the scintigraphic study permits its application, along with other such indicators of ischemia as stress electrocardiography and stress blood-pool scintigraphy, to the determination of the physiological significance of a coronary lesion visualized on angiography. While the advantages of stress perfusion scintigraphy over stress electrocardiography have been fairly well delineated, a comparative evaluation of the diagnostic sensitivity of perfusion scintigraphy and stress blood-pool scintigraphy is still under investigation. A scintigraphic functional evaluation appears to assess more thoroughly the degree of vascular involvement.[5] It also has special clinical applications as an aid for assessing the degree of functional impairment and for charting the course of therapy in patients with valvular heart disease.[6]

Although possessing a high degree of diagnostic accuracy and excellent specificity for recognizing coronary disease, stress perfusion scintigraphy lacks the level of sensitivity needed for making a judgment based only on negative test results. Therefore, the test is best used for patients with atypical pain; for those with equivocal stress test results in the presence of conduction abnormalities, ventricular hypertrophy, drug or electrolyte abnormalities; for those with borderline or ambiguous stess test results, or for any patient with a difficult or conflicting spectrum of diagnostic symptoms and signs of coronary disease. While scintigraphic findings in such cases cannot guarantee a correct diagnosis, they can help to clarify equivocal results, thereby pointing the way toward a correct diagnostic and future therapeutic course.[7] Scintigraphic results must not be accepted in a vacuum but must be evaluated in the light of associated clinical data. Scintigraphy often provides objective diagnostic information which is complementary to that of stress electrocardiography. In general, positive findings on a stress scintigram and stress electrocardiogram provide a higher degree of diagnostic certainty regarding the presence of coronary disease than does either test result alone; and negative stress scintigraphic and electrocardiographic results at optimal stress virtually exclude a diagnosis of coronary disease. Regardless of the findings on stress electrocardiography or stress scintigraphy, any decision to proceed with invasive diagnostic evaluation or medical treatment should depend on the entire spectrum of clinical data as derived from the history, physical examination and other test results.

To increase the diagnostic sensitivity of stress perfusion scintigraphy, a variety of computer enhancement methods have been devised. These methods have improved diagnostic sensitivity, at the expense of a somewhat reduced specificity.[8] Although such computer methods frequently provide increased overall accuracy and aid in quantitation of scintigraphic abnormalities, this loss of specificity should be kept in mind. Tomographic methods, also undergoing investigation, may also aid in diagnostic accuracy and quantitation of perfusion scintigraphic abnormalities.

While perfusion scintigraphic abnormalities at rest are relatively nonspecific and may indicate remote infarction, acute infarction or ongoing ischemia, the method can be useful in excluding a diagnosis of acute infarction if carried out soon after the onset of chest pain.[9] Furthermore, quantitation of such perfusion scintigraphic abnormalities has provided an extremely valuable prognostic index of the patient's condition shortly after acute infarction.[10] The variability in the size of such defects following the acute event shows promise as a marker of acute infarct size as well as of related, peri-infarction ischemia—important therapeutic and prognostic measurements for an accurate diagnosis of the patient's disorder. In addition, rest perfusion scintigraphy can be useful for the diagnosis of remote infarction, especially in the presence of a negative or ambiguous history or electrocardiogram.

Like other scintigraphic techniques used to evaluate the heart, perfusion scintigraphy, both at rest and with stress, requires a significant investment of personnel, equipment, time and effort.

These tests require a high degree of quality control and should be used only after due consideration, planning, and acquisition of the personnel and materials required to do a satisfactory job. The proper performance, interpretation and clinical application of perfusion scintigraphy and other nuclear cardiology studies should involve personnel trained in nuclear medicine, cardiology and, in some cases, computer science. The widespread clinical use of nuclear cardiology techniques, and the increasing availability of software packages, minicomputers, state of the art scintillation cameras and necessary radioactive pharmaceutical

agents, has prompted increased use of perfusion scintigraphy in nuclear medicine departments in university and community hospitals throughout the United States. However, judging from our own experience and from those of others at institutions, where perfusion scintigraphy and nuclear cardiology techniques have been firmly established as important clinical tools, the proper performance, analysis and clinical application of these methods best involves the combined, cooperative effort of nuclear medicine and cardiology personnel. It is only with the combined expertise of both disciplines that nuclear cardiology methods can achieve their optimal use and that clinical cardiologists and cardiac patients alike can reap the full benefits of perfusion scintigraphy and other developing methods of imaging.

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CASE REPORTS

Refer to: Brutoco RL, Spencer MJ: Tuberculous otomastoiditis: An old disease renewed. West J Med 133:69-71, Jul 1980

Tuberculous Otomastoiditis: An Old Disease Renewed

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INFECTION OF THE MIDDLE EAR is a familiar diagnosis to pediatricians. As many as 84 percent of children have otitis media at some point during infancy or childhood.[1] The usual acute pathogens are also well known to physicians. It is not so well appreciated, however, that *Mycobacterium tuberculosis* is still occasionally associated with middle ear suppuration.

Tuberculous otitis media was first described in the early 19th century, long before Koch's discovery of tubercle bacilli in 1882.[2] In the first three decades of this century, otic tuberculosis accounted for 2 percent to 15 percent of pediatric suppurative otitis.[3,4] With sterilization of milk and advances in the diagnosis, prevention and therapy of tuberculosis, the incidence of tuberculous otomastoiditis has become rare in the United States. Tuberculosis of the middle ear does, however, continue to occur, particularly among immigrants from less developed countries, and numerous cases have been reported in this country in the past 20 years.[5-13] The following cases illustrate the characteristic features of the disease.

Reports of Cases

CASE 1. A 16-year-old Mexican-American boy was referred to the University of California, Los Angeles, outpatient department by the school nurse for evaluation of a hearing loss. The patient had immigrated to the United States from Mexico in the past year. He had reportedly been healthy until 5 years of age, when a large pimple was noted over the area of the right mastoid. The lesion drained purulent material and resolved in several weeks. Meanwhile, a thick, green, odorless fluid began to drain from the right ear canal, which continued to drain intermittently for the next 11 years, in spite of multiple courses of both local and oral antibiotic therapy. Hearing loss was first noted by teachers when the boy was 7 years old.

A physical examination showed a well-developed adolescent with a purulent, greenish, odorless drainage observed in the right external auditory canal. The periphery of the drum was scarred and moderately vascularized, and a large perforation of the right tympanic membrane was noted. The malleus was not visualized, and exuberant "popcorn-like" tissue was noted in the superior-anterior portion of the field. A standard 5 TU (tuberculin units) purified protein derivative (PPD) tuberculin skin test was positive with 20 mm induration at 48 hours.

A 20 to 55 dB hearing loss in the right ear was noted, and audiometry confirmed unilateral incapability of auditory discrimination at all frequencies with total right-sided deafness at frequencies greater than 1,000 Hz. A roentgenogram of the chest showed a calcified granuloma in the upper right lung field and mastoid films disclosed sclerosis of the right mastoid. Temporal bone tomograms indicated an absence of distinct middle ear structures, but showed general sparing of the inner ear. Culture of the ear drainage on Löwenstein-Jensen medium grew *M tuberculosis*, sensitive to all tested antituberculosis agents.

Treatment with INH (isonicotinic acid hydrazide; also called isoniazid), rifampin, and ethambutol was initiated, and on follow-up examination six months later the patient was asymptomatic. Repeat audiometric testing showed a profound hearing deficit in the right ear. Both parents and four siblings also had positive intermediate (5 TU) tuberculin skin tests, and they all were treated with INH for a year. Although no active tuberculosis was found in the family, both parents had roentgenograms that suggested previous intrathoracic tuberculosis.

CASE 2. A 6-year-old Mexican-American girl

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was seen in the outpatient clinic with a seven-month history of limping of the right leg. On admission to hospital for workup of possible tuberculous osteomyelitis, it was noted that she had a green, odorless fluid draining from the left ear, in addition to a perforation of the left tympanic membrane. *Mycobacterium tuberculosis* was isolated from both the otic drainage and the bone. Her intermediate strength (5 TU) tuberculin skin test measured 20 mm of induration and an x-ray study of the chest showed an apical left lower lobe infiltrate consistent with tuberculosis. The child had severe hearing loss on audiologic screening. INH and rifampin therapy was initiated. When she reappeared six months later the otorrhea had stopped, and culture of the ear for *M tuberculosis* was negative. Four of her nine siblings and both parents had positive (5 TU) tuberculin skin tests.

Discussion

Tuberculosis remains a cause of significant morbidity and mortality.[7] Although effective antituberculous therapy has long been available, recognition of extrapulmonary tuberculosis continues to be difficult.[2] Indeed, the failure to consider this disease in the absence of respiratory symptoms may explain the unchanging incidence of extrapulmonary tuberculosis in recent decades, despite the decline in active pulmonary tuberculosis during that period.[8] It is important that physicians in the western United States be aware that persons of Spanish-American and American Indian descent have a significantly higher incidence of extrapulmonary tuberculosis.[8,9]

Because tuberculous otomastoiditis is relatively rare, the diagnosis is seldom considered in cases of chronic otitis media, and many cases progress unrecognized for prolonged periods, as exemplified in the two cases above. Both cases illustrate the usual features of this disease, which include the following: (1) painless otorrhea, (2) a rapidly enlarging perforation of the tympanic membrane (the initial stage of multiple perforations has generally progressed to coalescence by the time of presentation), (3) early and profound hearing deficiency, (4) abundant granulation tissue with necrosis of the ossicles and temporal bone, (5) an infectious process unresponsive to therapy for acute otitis media and (6) a positive tuberculin skin test.

Fever is uncommon in uncomplicated cases. Regional adenopathy is occasionally present and may be pronounced in infants.[10,14] Tuberculous otitis media in children is often associated with complications and tuberculous involvement of the mastoid is not uncommon.[2,3] Hearing loss occurs early in the course of this disease. Involvement of the labyrinth is also common and may be partially responsible for the profound hearing loss, but vestibular dysfunction is rare, presumably because the destruction is a gradual process.[9,11] A characteristic complication in infants is facial nerve palsy, a process which often resolves as the otitis is treated.[7,9] The most serious complication is tuberculous extension to the meninges, which may occur at any time in the course of the otomastoiditis.

Diagnosis of tuberculous otomastoiditis requires a high index of suspicion. Painless otorrhea in a patient with tuberculous infection elsewhere should be considered tuberculous otitis until proved otherwise. The clinical features as described above that occur in any patient should alert physicians to a possible tuberculous cause of the condition, particularly if the patient has lived in a low socioeconomic environment or has immigrated from a foreign country where tuberculosis is endemic.

Mastoid films may disclose destruction of temporal bone and well-pneumatized air-cells, but are not specific for tuberculosis.[2,4] A positive (10 mm or greater induration) 5 TU skin test may be helpful, but a negative test does not rule out tuberculosis.[11] Acid-fast bacilli observed on Ziel-Neelsen stain of otorrheal fluid is strong presumptive evidence of a tuberculous cause.[10,15] Confirmation of the diagnosis of tuberculosis is made by culture of the otic discharge, and microbial sensitivity testing is necessary for proper pharmacotherapy.[3,6] Multiple specimens are advisable because the number of organisms present may vary.

An essential component of management is to search for the primary focus of tuberculous infection. Primary infection may occur in infants and young children drinking unpasteurized cow's milk or nursing from women with generalized tuberculosis, with subsequent transport of *M tuberculosis* organisms by way of the eustachian tube. This presentation is rare in the United States today. Secondary infection, the usual mechanism of tuberculous otomastoiditis, results from hematogenous spread to the mastoid or via the eustachian tube through transport of autocontaminated sputum. The primary focus may resolve before presentation, as was the case in our first patient.

Household members should have tuberculin skin tests done as well because the initial contact is usually an adult in the household.

In view of the permanently destructive nature of the disease process, it is important to initiate therapy as soon as possible, with three first-line antituberculosis medications (such as INH, ethambutol, rifampin and streptomycin). Chemotherapy may be altered when sensitivities are determined; however, two-drug therapy is warranted for at least a year. Adherence to a therapeutic regimen of appropriately selected antibiotics effectively halts the disease process. Following successful pharmacotherapy, surgical intervention may be considered for many patients, particularly those who had a prolonged course of illness before effective treatment.[16] Necrotic tissue may be removed via a mastoidectomy.

Tuberculous otitis is a condition readily amenable to appropriate antituberculous chemotherapy. In any otitis which does not respond to the usual antibiotic therapy, or which presents as a painless otorrhea, tuberculosis must be suspect, and PPD testing should be routinely done in these patients. Most of the hearing defict present at the time of initial treatment will be permanent, but further loss can be prevented and progression to a life-threatening meningitis aborted.

Summary

Tuberculosis is a rare cause of middle ear suppuration in the United States today, although with an increase in foreign travel and migration there has been a recent rise in the number of cases, especially of extrapulmonary tuberculosis. In patients presenting with chronic, painless otorrhea or chronic otitis media that does not respond to the usual antibiotic therapy, tuberculous otitis should be considered. The diagnosis is important as tuberculous otomastoiditis is a rapidly progressive, irreversibly destructive process, and effective therapy should be instituted early. The two cases described above represent the characteristic features of this disease and illustrate the severe hearing deficiencies that can result in children. Tuberculous otitis media has been associated with serious consequences, including rapidly progressive permanent deafness and progression to fatal meningitis.

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Hypercalcemia, Pneumothorax and Pneumoperitoneum in a Patient With Pulmonary Mycobacteriosis and Esophageal Carcinoma

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ALTHOUGH CARCINOMA of the esophagus remains one of the least common of all malignant conditions to afflict people in the United States, its prevalence and age-adjusted death rate has been rising slowly but steadily over the past 50 years, particularly among nonwhite Americans. Based on death rates from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program (1973 through 1976), the esti-

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Figure 1.—Roentgenogram of the chest, with the patient upright, on May 28, showing bilaterial infiltrates with right upper and left lower lobe cavitation.

mated mortality from esophageal cancer in 1979 will be 8,400 in a total of 395,000 cancer deaths (2.1 percent).[1] The rising mortality has been attributed to increased longevity and better case-finding techniques.

About 80 percent of esophageal carcinomas present as obstructing lesions. Symptoms, however, frequently appear late.[2,3] When obstruction is absent, symptoms may arise as a result of extension of the carcinoma to contiguous structures or metastasis to distant sites, thus delaying diagnosis further.

This paper presents a case of esophageal carcinoma in which several uncommon features prevented physicians from making a precise diagnosis. The carcinoma occurred in a patient with underlying pulmonary mycobacteriosis. Of particular interest was the chest barotrauma which accompanied the terminal stages of the patient's illness.

Report of a Case

Ten days after receiving an aortobifemoral bypass graft for Leriche syndrome at another hospital, a 44-year-old Cuban man was readmitted to hospital in May 1978 with a four-day history of productive cough and fever.

As a youth, the patient had been told he had pulmonary tuberculosis. A few years before admission, a roentgenogram of the chest taken at a public health clinic showed "scarring at the right apex." He had a history of 60 pack-years of cigarette smoking as well as 15 years of heavy alcohol consumption and the presence of peptic ulcer disease, for which he took antacids. Recently, he had noted loss of appetite and substernal discomfort on eating. He had lost an unknown amount of weight during the six weeks before his operation.

A physical examination showed a thin man who appeared to be in no distress. Temperature was 37.6°C (99.6°F) and respirations 24 per minute. An examination of his lungs disclosed bilateral rhonchi. Hemoglobin was 9.9 grams per dl. The leukocyte count was 15,300 per cu mm with 79 percent polymorphonuclear cells, 3 percent band cells and 7 percent eosinophils. A roentgenogram of the chest showed a right apical infiltrate with cavitation and pleural thickening. Cytologic examination showed atypical cells not further classified. Sputum culture yielded *Proteus mirabilis* and *Candida* species. The patient was given chest physiotherapy, and penicillin, ampicillin and gentamicin were administered. He continued to lose weight and remained febrile, while chest roentgenograms showed development of bilateral alveolar infiltrates with cavitation in the left lower lobe. When sputum concentrates yielded acid-fast bacilli, he was transferred to Rancho Los Amigos Hospital on the 14th hospital day.

On admission to Rancho Los Amigos Hospital, a physicial examination showed the patient to be cachectic, but apparently in no acute distress. Temperature was 37.4°C (99.4°C), blood pressure 110/72 mm of mercury when supine, and 100/70 mm of mercury when sitting; pulse 104 beats per minute and respirations 18 per minute. Mucosae were pale, teeth were carious. The lungs were clear. There were no murmurs or gallops. Pulses in distal legs were diminished. There was a well-healed midline abdominal scar. Concentration was poor and there was slurring of words.

The hemoglobin value was 10.5 grams per dl and hematocrit 33 percent. The leukocyte count was 29,900 per cu mm, with 68 percent polymorphonuclear cells and 22 percent band cells. The platelet count was 347,000 per cu mm. Analysis of the urine showed trace protein, 5 to 10 leukocytes, 5 to 10 erythrocytes, and 10 to 20 hyaline and fine granular casts per high-power field.

Serum potassium was 4.9, sodium 135 and chloride 96 mEq per liter; blood urea nitrogen was 23, creatinine 0.8, glucose 118, calcium 13.4, phosphorus 3.1, magnesium 2.4 and uric acid 6.3 mg per dl; albumin was 2.5 and total protein 7.0 grams per dl; serum glutamic oxaloacetic transaminase (SGOT) was 28 (normal 7 to 40 mU per ml), lactic dehydrogenase (LDH) 177 (normal 100 to 224 mU per ml) and alkaline phosphatase 164 mU per ml (normal 30 to 85 mU per ml) and total bilirubin was 0.5 mg per dl. Serum protein electrophoresis showed depressed albumin, elevated α_1-globulin and broad band γ-globulin fractions.

Determinations of arterial blood gases while the patient breathed room air were as follows: oxygen pressure (Po_2) 53 and carbon dioxide pressure (Pco_2) 42 mm of mercury, pH 7.53 and bicarbonate 35 mEq per liter. A roentgenogram of the chest showed extensive patchy infiltrates bilaterally with cavitation in the right upper lobe. An electrocardiogram showed right atrial enlargement and changes consistent with chronic lung disease. Sputum culture grew *Proteus mirabilis,* but a urine culture yielded no growth. Sputum concentrates showed numerous acid-fast bacilli, and culture grew *Myobacterium avium-intracellulare* complex. Urine culture for acid-fast bacilli did not grow organisms. A lumbar puncture showed a normal opening pressure, no leukocytes, one erythrocyte per cu mm, and normal protein, glucose and glutamine concentrations.

The patient was treated with INH (isoniazid), ethambutol, and copious fluids given orally. His course was complicated by persistent hypoxemia, confusion, hypercalcemia and upper gastrointestinal bleeding. On the 17th hospital day, fever, hypotension and tachycardia suddenly developed. A repeat roentgenogram of the chest showed further extension of the left lower lobe infiltrate with cavitation (Figure 1). The patient was treated with nasogastric suction, antacids, penicillin, gentamicin, packed erythrocytes and intravenous fluids. Serum calcium rose to 14.6 mg per dl. Serum phosphorus was 2.4 mg per dl and chloride was 107 mEq per liter. Serum-intact parathyroid hormone (PTH) concentration by radioimmunoassay was 159 pg per ml. Normal range of PTH for serum calcium levels of 8.8 to 10.0 mg per dl is 255 ± 2 SD or 92 pg per ml, using an antiserum specific for intact PTH molecule, as measured by Laboratory Procedures, Esoteric Center, Kalamazoo, Michigan.

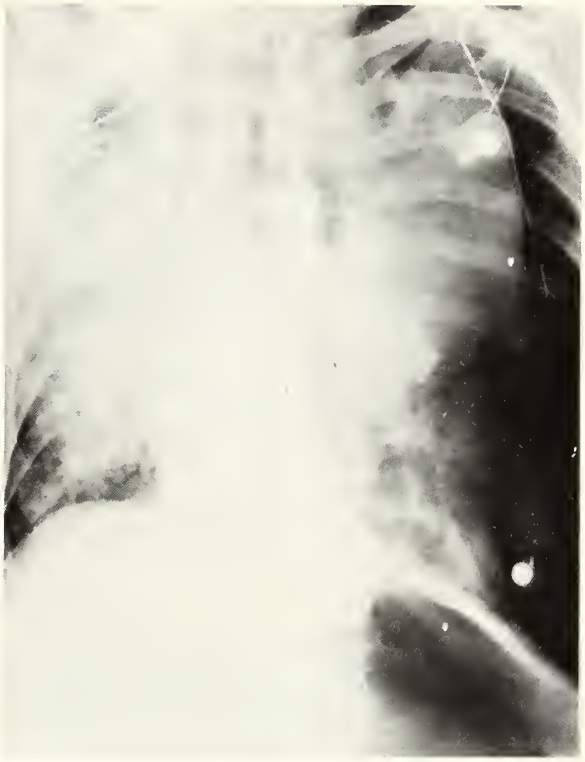

Figure 2.—Roentgenogram of the chest on June 2, showing large pneumothorax and pneumoperitoneum.

A liver scan on day 21 showed hepatomegaly with numerous filling defects. That evening the patient became acutely cyanotic and tachypneic. Secretions became copious. With the patient breathing room air, arterial blood gas determinations were Po_2 34 and Pco_2 60 mm of mercury and pH 7.22 A roentgenogram of the chest showed increasing consolidation throughout the left lung. Despite endotracheal intubation and assisted ventilation, respiratory function deteriorated.

On the 22nd day, the patient became hypotensive. The chest was hyperresonant on the left side with absent breath sounds. Another roentgenogram of the chest showed a large pneumothorax on the left, and free air under the diaphragm (Figure 2). During insertion of a tube into the chest ventricular tachycardia and fibrillation developed. The arrhythmia could not be corrected and the patient died despite resuscitation attempts.

Findings at Autopsy

At autopsy, a large, gritty, granular mass with central necrosis was found in the lower third of the esophagus. It infiltrated the wall and perforated into the trachea, mediastinum and left lower

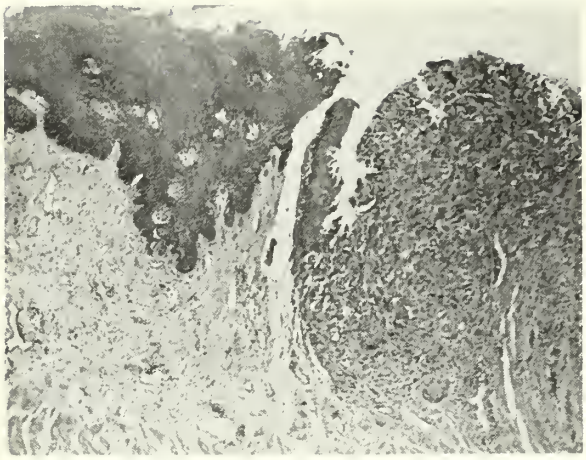

Figure 3.—Esophagus, with normal epithelium at left being abruptly replaced by infiltrating squamous cell carcinoma. This area was interpreted as the primary site. (Hematoxylin-eosin stain; reduced from magnification ×100.)

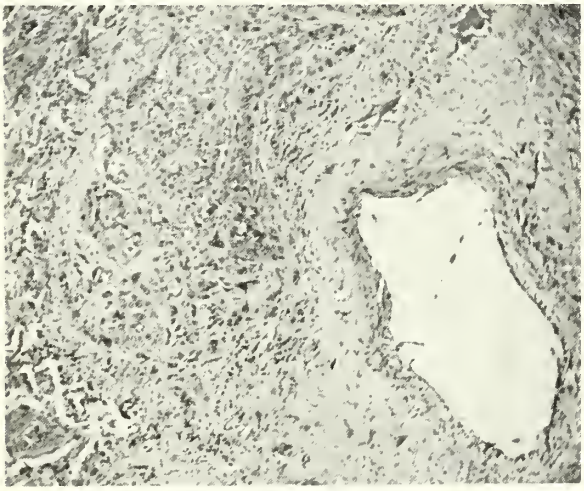

Figure 4.—Vessel in lung, with numerous nests of epidermoid carcinoma in periadventitial lymphatic channels. Tumor has infiltrated surrounding lung parenchyma and produced a metastatic mass. (Hematoxylin-eosin stain; reduced from magnification ×40.)

lobe. The tumor had formed a large mass with central cavitation which, in turn, communicated with the esophagus, trachea, lung and mediastinum. It had perforated the diaphragm. Histologic examination showed a mucoepidermoid carcinoma. In one area, it showed continuity with the squamous epithelial lining of the esophagus and invasion into the esophageal wall (Figure 3). There were metastatic lesions in both lungs, mediastinal nodes, liver, adrenal glands, kidneys, pancreas and myocardium.

Both lungs showed multiple cavities with caseation necrosis and typical tuberculous granulomata. Pneumonia, abscess formation, bronchiectasis and emphysema were widespread. Connection of the tumor masses with the trachea or bronchi was demonstrable, except in the area of the trachea contiguous with the lower esophagus. The neoplastic masses showed an epidermoid pattern. They were located at the periphery of the lung, often around a vessel which at times showed neoplastic cells in the lymphatics (Figure 4).

No evidence of metastasis was found in sections of vertebral bone (C-4 to coccyx). The distal aorta and iliac arteries were occluded by thrombi although the aortoiliac prothesis was patent. The parathyroid glands were not enlarged and were normal on microscopic examination. The brain and spinal cord were normal.

Discussion

Hypercalcemia

There are several unusual aspects of this case. First is the hypercalcemia which contributed to the patient's mental deterioration. Because the serum albumin was low, the proportion of unbound calcium ion was relatively increased, further augmenting his obtundent condition.

Hypercalcemia occurs in 16 percent to 56 percent of patients with carcinoma of the esophagus.[4] Some investigators feel that as many as two thirds of these cases are associated with ectopic parathyroid hormone production.[5] Others have been skeptical, citing the role of osteoclast-activating factor, prostaglandin E, sterols with vitamin D-like activity and immobilizaton.[4,6,7]

The cause of the hypercalcemia in this patient was probably ectopic PTH produced by the neoplasm, because he had no demonstrable bone metastasis and had an inappropriately high serum level of immunoreactive PTH for the degree of hypercalcemia manifested. The parathyroid glands were microscopically normal, ruling out primary hyperparathyroidism. Had the hypercalcemia been due to bone metastasis or other humoral factors, the concentration of PTH would have been undetectable.[8,9] In addition, near the end of his hospital course a high serum chloride to phosphorus ratio ($Cl/PO_4 = 107/2.4 = 40.4$) developed in the patient. Palmer and others have reported that the chloride to phosphorus ratio is higher than 33 in most patients with primary hyperparathyroidism as opposed to those with other causes of hypercalcemia.[10] Furthermore, they suggest that patients with ectopic PTH-producing tumors also

have high chloride to phosphorus ratios. A rise in the patient's phosphorus concentration would have suggested suppression of PTH by hypercalcemia induced by skeletal metastasis.[8] Increased urinary excretion of cyclic adenosine monophosphate (3′5′-cAMP) expressed as a function of glomerular filtration has also been found to be a very useful test indicative of excessive amounts of circulating active PTH.[11] Demonstration of PTH in the neoplastic tissue would have provided unequivocal proof of its source; however, these studies were not available.

The radioimmunoassay of PTH in our patient made use of the intact, biologically active form in the circulation. Benson and colleagues, and Hawker and Di Bella have found the radioimmunoassay to be useful in differentiating ectopic hyperparathyroidism due to neoplasia from primary hyperparathyroidism.[8,12] The COOH-terminal, biologically inactive fragment of the PTH peptide, which was not measured directly in our patient, is greatly decreased in ectopic hyperparathyroidism as compared with primary hyperparathyroidism. On the other hand, the quantity of circulating intact parathyroid hormone is similar in both groups.[8] Because intact PTH was measured in our patient and because this assay recognizes COOH-terminal fragments to a much lesser extent, it would explain why the assay would give a lower PTH level in a patient with suspected ectopic hyperparathyroidism than in a patient with primary hyperparathyroidism. Hawker and Di Bella have concluded that (1) the blood of patients with ectopic hyperparathyroidism contains predominantly intact immunoreactive PTH and (2) the blood of patients with primary hyperparathyroidism contains a form of immunoreactive PTH that is either not detected or is found only in small quantities in ectopic hyperparathyroidism, and that this is probably the COOH-terminal fragment.[13]

Riggs and others have suggested that nonendocrine tumors associated with hypercalcemia produce a larger (precursor) PTH molecule and this precursor may not be converted to a smaller form in these patients.[14]

Formation of Fistulas

The most common presenting symptom of esophageal carcinoma is dysphagia, a complaint that our patient had described vaguely.[2] However, about 20 percent of malignant lesions are nonobstructing when first detected.[3] When dysphagia is absent, unusual presenting symptoms may occur. For example, local extension can cause hoarseness due to involvement of the recurrent laryngeal nerve.[3] The incidence of esophagorespiratory communications is 5 percent to 10 percent.[15] Most such fistulas occur in the middle third of the esophagus, and are a result of spontaneous or radiation-induced necrosis of the tumor adjacent to the trachea or major bronchus. Our patient's condition was unusual in that the esophagobronchial fistula occurred in the lower third of the esophagus. Such patients, who are already suffering from advanced esophageal cancer and its treatment, begin to have sudden bouts of coughing, chest pain, hemoptysis, aspiration, pneumonia or sepsis.[3,15,16] The most common cause of death in patients with esophagorespiratory fistulas is not from the cancer itself, but from aspiration.[16] Treatment is difficult, and at best, palliative.[15,16]

When such a fistula is the result of a neoplasm, a question may arise as whether the tumor originated in the esophagus or the bronchus. Indeed, at our patient's autopsy, the presence of a large mass in both trachea and esophagus invading the mediastinum, pericardium and diaphragm initially gave the impression of a primary bronchogenic carcinoma, also suggested by the pattern of metastasis. However, careful dissection and histologic examination showed the site of origin in the esophagus, and failed to find any such foci in the tracheobronchial tree. The location and pattern of the nodules in the lungs also suggested their metastatic nature. In fact, it is rare for esophageal symptoms to develop as a result of invasion of the esophagus by bronchogenic carcinoma even late in the disease.

Barotrauma

The development of pneumothorax and pneumoperitoneum is very unusual in a patient with esophageal carcinoma and pulmonary mycobacteriosis. Chronic bronchitis and emphysema are the most common causes of spontaneous pneumothorax in patients over 40 years of age.[17] Less commonly, rupture of a caseating subpleural tuberculous lesion may lead to pneumothorax. Even more rare are pneumothoraces associated with intrathoracic neoplasms.[17] Metastatic sarcomas are the most common neoplasms associated with spontaneous pneumothoraces[18,19]; bronchogenic carcinoma is a rare cause.[20,21] A pneumoperitoneum associated with a *supradiaphragmatic*

neoplasm has not been previously reported. Likely mechanisms for these phenomena in our patient include:

- Rupture of a subpleural bleb in an area of emphysema or granulomatous cavitation, which may be facilitated by positive pressure ventilation.
- Invasion of the esophageal neoplasm into the lung parenchyma with subsequent rupture through the diaphragm into the peritoneal cavity.
- Direct invasion of the pleura by the esophageal neoplasm with necrosis, rupture or perforation.
- Air, forced into the lungs under high pressure, may rupture alveoli and dissect into the interstitial space or perivascular sheaths.[22,23] From here, it may dissect toward the hila, mediastinum and through the diaphragm into the retroperitoneal space. If air flow continues, the retroperitoneal space ruptures, releasing air into the abdominal cavity. On a roentgenogram of the chest (with the patient in an upright position), it can be noted that intraperitoneal air rises to the highest point below the dome of the diaphragm. It can be distinguished from retroperitoneal air which is at greatest volume medial or lateral to the highest point of the diaphragm.[24,25]

Pneumoperitoneum has been described most frequently in infants with respiratory distress syndrome who are treated with positive pressure ventilation.[26-29] Recently it has also been described in adults receiving assisted ventilation.[24,30] Usually a pneumothorax occurs before the pneumoperitoneum.[24,26] Pneumoperitoneum without evidence of pneumothorax favors a diagnosis of perforated intraabdominal viscus. However, when the two coexist, a perforation cannot be ruled out. A rupture of the gastrointestinal tract would be suggested by air-fluid levels seen intraperitoneally on a roentgenogram of the patient in an upright position,[31] and can be verified by administration of a water-soluble contrast material.

Had the patient's condition permitted, further diagnostic studies such as esophagography, esophagoscopy and bronchoscopy would have led to the precise diagnosis and, perhaps, an explanation for the radiographic findings. Unfortunately, inanition, hypercalcemia and rapid progression of respiratory failure prevented such investigations.

In conclusion, esophageal cancer can present with uncharacteristic clinical, laboratory and radiographic findings, and not all patients will have dysphagia and aspiration when first seen. Physicians who are aware of the pathophysiological events that occur with this disease will be better prepared to deal with them, if only to allow the patient's decline to be more tolerable.

Summary

Coughing and fever developed in a 44-year-old man shortly after an aortofemoral bypass operation. A roentgenogram of the chest showed bilateral infiltrates with cavitation. The patient's course of illness was complicated by hypercalcemia, progressive obtundation and respiratory failure, making assisted ventilation necessary. Shortly before death, pneumothorax and pneumoperitoneum developed. At autopsy, findings included active pulmonary disease due to *Mycobacterium avium-intracellulare* complex and esophageal carcinoma invading the lung, mediastinum and diaphragm.

Hypercalcemia, an unusual feature of esophageal cancer, was probably caused by ectopic production of parathyroid hormone, which was shown to be present in the serum by radioimmunoassay for the intact molecule. The most unusual aspect of this case was pneumothorax, occasionally reported with intrathoracic tuberculosis and neoplasms, and pneumoperitoneum. Mechanisms that can account for these phenomena were discussed.

While dysphagia is the most common presenting symptom of esophageal cancer, physicians should also be aware of these unusual manifestations.

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Evaluating Thyroid Nodules

THE CRITERIA that are most helpful in evaluating thyroid nodules are their size, shape and consistency. Nodules that are over 2 to 2½ cm, that by their consistency suggest anything of a hard or infiltrating quality, and that have a rate of growth that is persistent and progressive, are nodules that should be removed. The sex of the patient is germane in this situation . . . more nodules are found in females than males. When there is a nodule in a male . . . there is an increased index of suspicion and a lower threshold for wanting to proceed with an operation. History of ionizing radiation is important. However, the present data suggest that these nodules can be evaluated in the same way as nodules in patients without a history of ionizing radiation. . . . If there is a history of ionizing radiation and one cannot feel any nodule . . . [I] would not get a scan. However, if a scan does show anything that is cold, this might lead to an operation. We have never seen a situation where nonpalpable lesions in the thyroid have caused any significant clinical disease.

—CALDWELL B. ESSELSTYN, JR., MD, *Cleveland*

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Orthodox Medicine Humanistic Medicine Holistic Health Care

IN THE DECEMBER 1979 issue the editors began a forum for discussing orthodox medicine, humanistic medicine and holistic health care. The response from readers has been so great that contributions to the forum no longer can be accepted. A future issue of the journal will carry a summary of the dialogue and discussion.

—MSMW

On the Etiology of the Holistic Pseudoschism

BARRY D. ORVELL, MD

I AM DEEPLY MOVED by the courage of the journal in having a forum about alternative health modes. The articles have been varied and impassioned. Your intent to heal the body of medicine has necessarily brought it to surgery instead of autopsy. And the letting of some bloody and inflamed writing is greatly appreciated by those of us in medicine who have been struggling with these important issues in silence. By way of comment, I wish to share my perception of the historical context from which this paper and others like it come.

There is a recent tension in the matrix of medicine which cannot be ignored. With the exponential growth of medical knowledge in the last half century, two things have happened. Doctors are being sued, and an increasing portion of the public is turning to alternative health modalities. What happened?

In earlier days, the physician was revered for his compassion above all else. By the warmth of his presence, he offered comfort and consolation to his patient and to each member of the patient's household. He shared in the common helplessness of man whose fate was determined by an indifferent universe. His sense of impotence was made all the more poignant by the sense of divine will as offered by the clergy. At the deathbed, both men stood. They struck a sense of balance in the universe and this must have had a profoundly soothing effect on the household. There was a time then to press hands in gratitude for our common humanity before leaving the household.

The advent of modern medical knowledge and technology allowed the man of caring to do more than wring his hands and press other hands. He became a man of doing. This doing increased steadily. He could do more in less time, and thereby help more people to get over their illnesses. He, the physician, became aware now of the shortage of time—time to learn more, time to do more, no time to rest. In other words, he became a very busy person. Thus, the man of compassion became rude at times.

In this frantic flow of events, the accruement of more knowledge and more power to cure silently rearranged our priorities. This process continues even now, with an accelerated pace, and we need to stop and take a look at where we are. We are more in our heads than in our hearts. It used to be the other way. There should be nothing incompatible between caring and curing. I believe that as physicians, we do care. But because of the imbalance of little time and big power, our caring got partially twisted, and our humanity got pushed aside just enough to be noticed. It is understandable that people became frightened and angered at this man who had no time to explain things to them.

Sometimes I think the public would prefer a return to the 19th century style of medicine. Sometimes I think people prefer love to longevity. Sometimes I think doctors and patients have differing ideas of the role of a doctor.

It is when I consider, side by side, these two simultaneous events—the rise of holistic medicine and the rise of malpractice suits—that I get such thoughts. Perhaps the bridge between mainstream medicine and holistic medicine is time, the time to care.

There is no cause for alarm. The message is not to tear down the Establishment. It is, rather, to join it, and breathe more life into it. We all share a common pulse.

Dr. Orvell is in the private practice of internal medicine and nephrology in Oakland, California.

Refer to: Orvell BD: On the etiology of the holistic pseudoschism, *In* Orthodox medicine, humanist medicine and holistic health care—A forum. West J Med 133:78, Jul 1980

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Patients' Life-styles and Health Care Costs

To the Editor: The May 1980 issue of the Western Journal contains several articles upon which I wish to comment. First, in regard to the article on preventive medicine by Dr. Chris Holmes and the related editorial, disease prevention and preventive medicine are concepts which *every* physician must concern himself with, if he is to practice good medicine. Most physicians do concern themselves with these concepts. They too often are wrongfully charged with practicing *only* curative medicine by those who do not understand what they are talking about. The problem facing the average physician is that many disease prevention measures relate to factors substantially beyond the control of the individual physician. They require societal and individual patient action.

Physicians can and do point out life-style measures that may make for less morbidity and mortality, but they cannot force people to smoke less, drink less, avoid drug abuse, eat more prudently, use less salt, enact fluoridation, exercise, use their seatbelts, avert unwanted conception, immunize their children, adopt effective and comprehensive health education curricula in their school districts, and so forth. Perhaps more physicians should take stronger roles in the community and spend more time educating and encouraging their patients and political leaders. I think they should—but, thus far, society has been slow to adopt what is being proposed. This is an issue that will always be with us—one hopes to a lesser degree in the future.

Health care cost containment (as discussed in the special symposium in the same issue) is another matter where physicians are continuously placed on the defensive. To suggest that physicians control 70 percent to 80 percent of personal health care expenditures (as stated elsewhere and quoted in the article by Sammons) is nonsense. It is the patient and his family who determine their own life-styles and who decide to seek health care. Life-style factors and the inevitable aging process are the major determinants of health care need and costs. A physician's ability to affect health care costs is in reality rather modest.

Once a patient comes to a physician's or hospital's door, he must be seen; fractures must be set; arthritis, cancer, diabetes, heart attacks and strokes must be treated; babies must be delivered; some of the aged must be placed in nursing homes and the dying must be attended to. Most of the protocols for dealing competently with these situations are fairly well established and, on a community-wide basis, careful physician attention to costs might shade those under their control by 5 percent to 10 percent at the most. Far more significant cost savings *on an age-specific basis* could be achieved by patient and community adoption of healthier life-styles. However, overall costs in such cases would continue to increase—the Fountain of Youth remains to be discovered.

MAX BADER, MD, MPH
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Unsolicited Advice for the Pharmaceutical Industry

To the Editor: My recent comments in the journal (Pill Packaging, Correspondence, May 1980) have been so enthusiastically received I have decided to favor the drug industry with another suggestion. Rather than simply placing an expiration date on a pharmaceutical product in accordance with federal code, *color code the date.*

A *red* date would imply that the product can become toxic with age. A date printed in *blue* ink would indicate that the product may become impotent with age and a *green* ink date would mean the product can be damaged by fire, flood, abrasion, traction, compression, etc. *Black* ink

would mean the manufacturer declines to imply any other meaning to the date stated.

ROBERT HAWKINS, MD
Santa Barbara, California

EDITOR'S NOTE: *Unsolicited advice is sometimes worth at least a moment's thought. But somehow green does not seem quite right for "fire, flood, abrasion, traction, compression, etc."*
—MSMW

Brompton Mixture Taken Intravenously by a Heroin Addict

TO THE EDITOR: We wish to report a case of illicit intravenous use of Brompton mixture in a known heroin addict.

A 38-year-old left-handed man was admitted to hospital because of confusion and lethargy following a sedative drug overdose. The next day his mental status was normal, but he was unable to move his right arm. The patient said that there had been no trauma to the arm, and that there was no pain. On examination there were numerous needle *tracks* in both arms and the neck. There was diffuse weakness, most severe proximally, of all the muscles of this right arm. There was no atrophy. The muscles of the left arm and both legs were normal. Deep tendon reflexes were absent in the right arm and normal in the left arm and legs. The plantar responses were flexor. Sensation to pinprick was intact, with hyperpathia in the right arm. Position sense, light touch and temperature sensation were diminished in the right hand and arm but normal elsewhere. Our impression was that the patient had acute brachial plexus neuropathy as a complication of intravenous injection of an adulterated opiate solution, a previously reported complication of heroin addiction.[1] However, the patient denied any use of heroin for the past several months. During that time he had administered approximately 30 ml of Brompton mixture twice a day intravenously, most recently using only the right arm.

The patient said he had purchased the solution from a friend with terminal cancer who received the medicine for relief of pain and who had sold it to earn money for his family. The patient stated that his wife and several acquaintances had also switched from daily heroin use to the use of Brompton mixture from the same source because it was cheaper ($30 per dose versus $100 per dose of the heroin) and had a more lasting effect.

Standard Brompton mixture contains varying amounts of morphine, cocaine, alcohol, water and flavoring syrup, and has proved useful in the treatment of pain in patients with cancer.[2] Physicians and others involved in terminal and hospice care should be aware of the possible diversion or resale of Brompton solution to heroin addicts.

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San Francisco

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Unusual Pelvic Pain Apparently Cured by Pelvic Examination

TO THE EDITOR: Although this is not a particularly scientific report, I feel that the histories given below are dramatic enough to justify publication in the hope of uncovering more, similar experiences.

Here, at the Oregon State University Student Health Center, in the last two years I have seen three female students who had essentially identical histories of sudden onset of severe lower abdominal pain. The pain was crampy, waxing and waning, and suprapubic in location. It was so severe that they were not able to walk without aid. On abdominal examination in all three there was tenderness in the suprapubic area, most severe somewhat lateral to the midline. Findings on physical examination in all three were normal, except for one-sided severe adnexal tenderness. In all three, during a gingerly but thorough bimanual examination, the pain suddenly and dramatically abated and did not return. In all three cases, the tender adnexal area was being probed at the time of the resolution of the pain.

Neither I nor my gynecologist colleagues can rationalize anatomically what occurred in these three patients that was so dramatically relieved by manipulation. However, it seems clear to me that these three cases are examples of some entity that is easily cured by gentle adnexal manipulation. One reason that this experience may be somewhat rare is that a clinician may be overly gingerly in pelvic examination for fear of rupturing an ovarian cyst or abscess, or stirring up pelvic inflammatory disease.

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Special Article

Measurement of Physicians' Performance Using Existing Techniques

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Existing techniques permit objective and valid measurement of limited elements of physicians' performance. These limited aspects, however, are of considerable importance to patients. The basic components of performance in medicine and surgery can be defined and used as the basis of organized programs for such evaluation. Interhospital comparisons can provide an effective impetus for assessing and improving performance of individual staff members when this is indicated. Professional auspices are needed for the development and application of methods that can provide continuing assurance that the clinical activity of physicians corresponds to contemporary standards.

A system of incentives should be provided to physicians to promote their participation in voluntary programs of self-assessment. The incentives should be in the form of performance assessment credits, comparable in definition to continuing medical education credits, but granted for participation in an accredited program that objectively measures physicians' performance against national standards of the respective specialty.

QUALITY OF MEDICAL CARE is superior to the extent that physicians correctly evaluate and effectively treat individual patients' medical problems with the least feasible risk, and provide the education, counseling and clinical caring that enable a patient to attain the full psychosocial as well as clinical benefits obtainable from medical care. The main determinant of quality or lack of quality in medical care is the individual physician's performance—that is, what he does with, for and to his patients, or arranges to have done, and the actual or probable results of those actions. If that performance is effective, outcomes attributable to medical care are beneficial; if ineffective, the patient receives less than full benefit of care or actually suffers from adverse outcomes.[1]

Performance differs from competence, which is the capability to perform effectively. This capability comprises knowledge and a variety of abilities which include skills, habits, attitudes, clinical judgment and problem solving.[2-4] The various

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components of competence can be measured directly or indirectly, but the validity of such measurements—that is, their relationship to actual performance in the care of patients—has not been established.[2,5,6] This paper addresses the following question: Can existing methods adequately measure physicians' performance?

Despite the widespread adoption of medical audit as an additional professional mechanism for maintaining high standards of care, existing methods of quality assurance have been judged ineffective in assuring that all practicing physicians provide an acceptable degree of care.[7-12] As one consequence, more attention is being directed to measuring the performance of individual physicians.[2,13-20]

Measurement of Performance and Its Effects

The limitations of existing methods make it impossible to evaluate all aspects of performance.[21] However, some of the most important elements can be measured, including their effects on patients. Performance is most readily and reliably measured in general surgery, using the methods developed over the past 60 years: clinical and tissue review to assess adequacy of diagnosis and

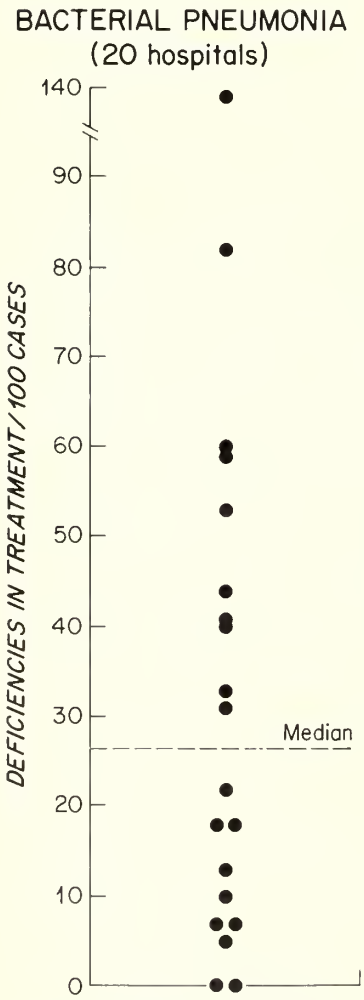

Figure 1.—Rates of inappropriate treatment in cases of acute bacterial pneumonia in 20 hospitals. Each dot = 15 or more cases.

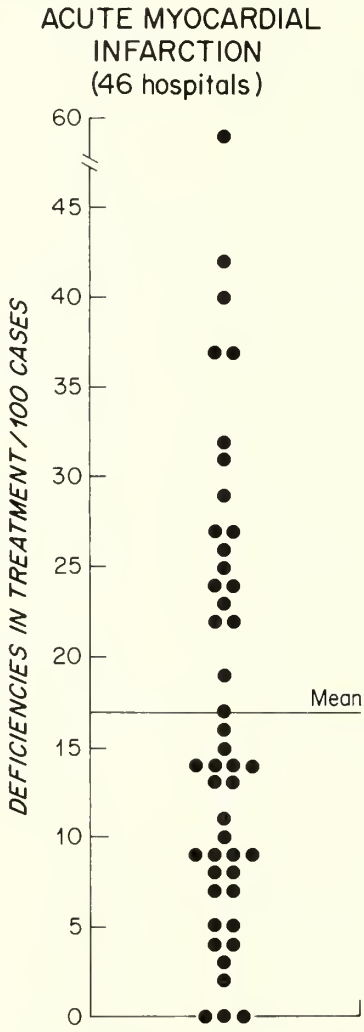

Figure 2.—Rates of inappropriate treatment of cases of acute myocardial infarction in 46 hospitals. Each dot = 20 or more cases.

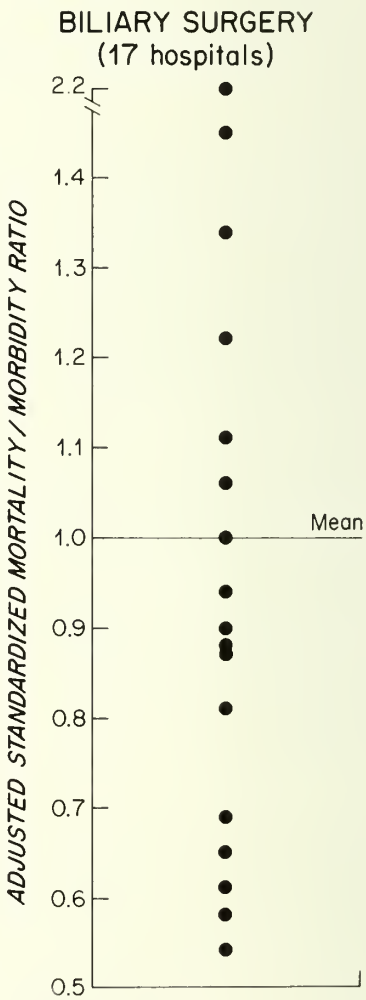

Figure 3.—Range of adjusted standard mortality and morbidity ratio after biliary surgery in 17 hospitals.[38] Mean value = 1. All values above 1 indicate a higher incidence of morbidity and mortality than could be attributed to the patient, diagnosis and operation variables listed in Table 1.

indications for operation, and review of postoperative complications and deaths.[22-26] The American College of Surgeons officially states that delineation of clinical privileges should be based on demonstrated performance, and the Joint Commission on Accreditation of Hospitals encourages this through its standards.[27,28]

Auditing was well established by the 1950's as an effective means of monitoring the performance of individual surgeons and gynecologists.[22,24,26] However, this fundamental purpose was lost sight of in the emphasis on "patterns of care," when auditing was widely extended to medically treated conditions during the 1960's. The rapid rise of medical (as opposed to surgical) audit between 1970 and 1976 was attributable to social, legal and political changes that profoundly affected the practice of medicine. The even more rapid fall of auditing between 1977 and 1979 can be traced to inadequate application of known principles and failure to appreciate its limited capabilities.[10,11,29,30]

Measurement of physicians' performance should be directed to those actions that have demonstrably or predictably beneficial results when correctly carried out or, conversely, have actual or potentially serious, adverse effects when not carried out properly. The categories of actions most frequently reported by internists and pediatricians to have important, direct effects on patients are (1) a correct, adequate diagnosis, (2) proper use of drugs, biologicals and electrolyte solutions, (3) adequate patient education and (4) appropriate physician behavior and attitude toward patients.[1] The most frequently reported patient outcomes attributable to effective performance are (1) improvement in clinical signs and symptoms, (2) increased functional capacity in daily activities, (3) positive attitudes toward their own condition and their physican and (4) increased compliance.

Establishing an adequate diagnosis in which problems presented by a patient are correctly defined is a self-evident, fundamental requirement for effective patient care. In both office and hospital practice, prescribing indicated drugs correctly is second in importance only to this. An extensive literature describes the continuing prevalence of inappropriate prescribing by physicians and the consequences of such actions.

Physicians' Performance in Hospital Care

Medical staffs have no dependable means of knowing how their actual performance compares with that of other medical staffs caring for comparable patients under similar circumstances. Valid comparative data are rare. Consequently, hospital staffs have little reason to believe that they are not performing at the level of technical excellence which the state of medical science makes possible.

In medically treated patients, provision of scientifically established methods of diagnosis and treatment is a valid indicator of the adequacy of performance. Definite associations can be shown between indicated procedures and expected outcomes and between contraindicated procedures and adverse outcomes if these causal relationships have been established by clinical research. Figure 1 illustrates the variations among the medical staffs of 20 hospitals in failure to determine the sensitivity of the causative organism or to prescribe antimicrobial agents accordingly in patients with verified acute bacterial pneumonia. Those patients not given the benefits of these two procedures had significantly worse clinical results.[31] Figure 2 shows the relative performance of 46 medical staffs in routinely administering saline solution intravenously or failing to provide proper antiarrhythmic therapy to patients with verified acute myocardial infarction who had survived the first 48 hours of their hospital stay. Those patients had a significantly higher death rate.[31]

In medically treated patients, immediate clinical outcomes or complications generally cannot be used as indicators of the technical quality of care because the age and general condition of patients strongly affect the immediate outcomes of hospital care.[32] Also, in individual hospitals, the relatively small number of patients with any one condition precludes finding an association between treatment and results. Instead, the more dependable measure of performance is adherence or nonadherence to scientifically validated methods of diagnosis and treatment. Adherence to these methods means that a physician has provided his patients with the highest probability of obtaining the full benefit attributable to medical treatment. The prevalence and serious consequences of inappropriate prescribing in hospital care indicate this is an important area of performance that can be readily measured.[33-37]

In surgically treated patients, the incidence of postoperative complications can be a de facto indicator of effectiveness of preoperative, intraoperative and postoperative evaluation and management. The important proviso is that all other

TABLE 1.—*Factors Predisposing to the Occurrence of Complications and Mortality After Biliary Surgical Operations**

Patient factors
Age, sex, socioeconomic level
Physical status
Level of stress
Emergency status
Diagnosis variables
Cholelithiasis
Acute cholecystitis
Cholelithiasis with acute cholecystitis
Gall bladder obstruction, fistula or perforation
Cholesterolosis or hydrops
Pancreatitis, acute or chronic
Operation variables
Cholecystectomy
Incision of bile ducts (exploratory)
Cholecystotomy
Excision of bile duct lesion or biopsy
Anastomosis or repair of bile duct
Cholecystography
Appendectomy
Liver biopsy

*Source: Stanford Center for Health Care Research.[38]

factors that influence the occurrence of complications be taken into account. Deaths occurring up to the 40th postoperative day may also be a valid indicator.[38] The Institutional Differences Study[38] identified a number of patient, disease and operation factors (Table 1) that were statistically related to the incidence of postoperative morbidity and mortality. After correcting for all of these circumstances, the study reported nearly a fivefold difference among the surgical staffs of 17 hospitals in patient morbidity and mortality after biliary operations[38] (Figure 3).

It is reasonable to ask whether the differences were all attributable to surgeons, even though the variables listed in Table 1 were taken into consideration. Some evidence bearing on this question is found in the cooperative study involving the surgical staffs of 95 hospitals.[39] They judged 30 percent of 2,941 postoperative deaths and life-threatening complications to have been preventable. Of these, 88 percent were attributed by those staffs to deficiencies in individual surgeons' performance in diagnosis, operative technique, judgment or postoperative care.

In carrying out interhospital studies for purposes of comparison, the data must be reliable, accurate, complete and genuinely comparable—that is, all other factors that could explain a seemingly substandard level of performance by one or more hospitals must be taken into account. Most important, the data must be perceived by the medical staffs as valid indicators of the adequacy or inadequacy of performance.[40] Given such data, medical staffs would be in a position to decide whether more direct assessment of performance by an individual physician or surgeon is indicated. Substandard performance of the staff, as reflected in valid interhospital comparisons, means that some staff members are not performing at the level required for retention of their current clinical privileges.

Physicians' Performance in Office Care

It has been reported that many patients under treatment for hypertension or other common conditions have not had the diagnosis confirmed by the usual observations and tests.[41,42] Similarly, the approach to prescribing drugs in office practice is reported to be uneven in quality.[43-46] Analyzing the prescribing habits of a physician is a dependable and the most generally applicable approach to assessing his or her performance in office care. Standards for the drug treatment of common conditions are increasingly available in the literature.[46,47] Assessing this aspect of performance determines the extent to which physicians are providing their patients with the highest probability of benefiting from modern drug therapy, while minimizing preventable adverse effects.

Other major elements of physicians' performance in office care are those that lead patients to cooperate in self-management, thereby increasing the likelihood of their achieving the optimum feasible outcomes.[48-51] These outcomes may be classified as clinical, functional, educational, attitudinal and behavioral (compliance). Reliable information on each of these categories can be an indicator of the effectiveness of care. *Clinical* outcomes are those attributable to receipt of efficacious treatment: control of hypertension, diabetes mellitus or common bacterial infections; relief from attacks of bronchial asthma; reduced symptoms of chronic obstructive pulmonary disease, congestive heart failure, angina pectoris or osteoarthritis. These are discrete, documentable impacts of rational drug and other therapy.

Functional outcomes are reflected in changes in the patient's ability to carry out his or her usual activities, whether in work, recreation, family responsibilities, school or community affairs. Williamson has reported on the extensive use of a simple scale that permits documentation of patients' functional status over time.[41] *Educational*

outcomes are the knowledge and understanding each patient has of his or her own condition and its treatment. These are necessary if patients are to benefit fully from ambulatory care. Equally important are patients' attitudes toward their own condition, their physicians and medical care in general. These attitudes indicate satisfaction with care and correlate highly with compliance.[50] There appears to be little relationship between patient satisfaction and technical adequacy of care.[52]

Office records usually contain little information on patient education, counseling and general support, or on how these factors affected the patient's overall condition.[53,54] It is therefore necessary to obtain data on these outcomes by interviewing patients themselves. Telephone surveys are feasible and acceptable.[55,56] Such interviews by telephone are economical and often provide more accurate and complete information than is obtained face to face or by a mailed survey.[56]

Physicians' Performance as Reflected in Medical Records

The completeness of medical records has been thought to reflect the quality of care actually received by patients.[48,57,58] However, that conclusion is based on studies that did not consistently require objective confirmation of diagnosis or evidence that treatment was (1) scientifically valid, (2) indicated in the individual patient and (3) correctly applied. However, these conditions were met in a study based on 6,946 hospital cases.[32] In that study, only 30 percent of the records contained the information needed for a definitive clinical evaluation, but 73 percent of those same records contained objective evidence that the patient had received appropriate, effective treatment. As shown in Figure 4, there was no relationship between the completeness of recording and the provision of correct treatment. Also, no correlation was found between the amount of recording and whether patients attained the immediate outcomes that could reasonably be expected from having received proper treatment. Until more definitive evidence becomes available, the completeness of recording by physicians should not be interpreted as a valid indicator of their performance.

Measurable Components of Performance

The measurement of individual physicians' performance must be based on objective, reliable and valid data. These requirements can be met in what might be termed the basic components of measurable performance. Table 2 lists these for surgically and medically treated conditions, respectively. Data on each of the components can be obtained from medical records, the work of standing committees of the medical staff and, in office care, from patient surveys. Standards for surgeons' performance are based on a combination of scientific and empirical reference points, best determined by specialists who are familiar with ongoing advances and with the factors that may influence the incidence, nature and severity of complications.[38,39] Standards for judging the care of medically treated patients are derived from specialists who are clinically active and are abreast of clinical research in their field. The

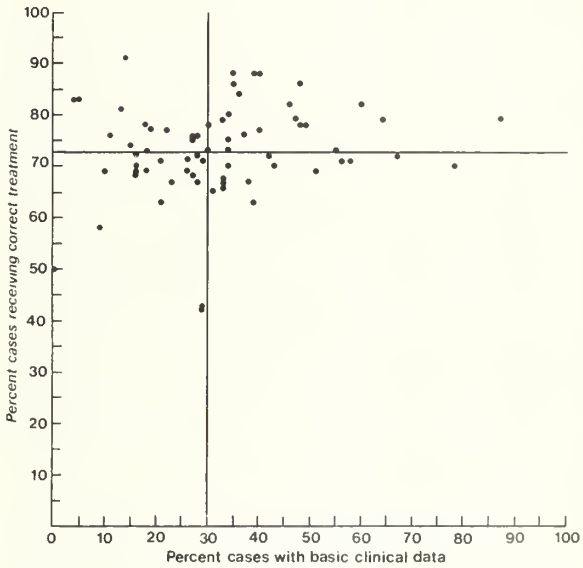

Figure 4.—Scatterplot illustrating lack of correlation between completeness of recording (median = 30%) and provision of correct treatment (median = 73%) in 6,946 cases in 68 hospitals.

TABLE 2.—*Measurable Components of Physicians' Performance*

In surgically treated conditions
- Objective substantiation of diagnosis and conditions requiring treatment
- Substantiation of indication(s) for operation
- Lowest feasible rate of preventable postoperative complications

In medically treated conditions
- Objective substantiation of diagnosis and conditions requiring treatment
- Correct application of validated treatment
- Avoidance of contraindicated treatment
- Attainment by patients of expected functional and psychosocial outcomes

TABLE 3.—*Completeness of Physician-Recorded Data in Patients' Charts Before and After Adoption of Forms Specifying Data Needed for Making Clinical Decisions*

Setting	*Percent Before*	*Percent After*
Medical clinic[60]	19	92
Student health service[62]	4	96
Emergency service[63]	4	86

TABLE 4.—*Percent of Patients Receiving Correct Treatment Before and After Adoption of Forms Specifying Data Needed for Determining Correct Treatment*

Setting	*Percent Before*	*Percent After*
Medical clinic[60]	17	55
Student health service[62]	43	82
Emergency service[60]	Unknown	86
Surgical service[64]	60	94

standards must be nationally applicable, except for unusual local circumstances.

Although the basic components as listed appear to be elementary, threefold to fivefold differences have been documented among medical staffs of various hospitals on these rudimentary elements.[20,32,38,59] This suggests that these components may suffice as the initial basis for measuring physicians' performance. They amount to a framework for collecting comparable data which can be analyzed to provide systematic, empirical descriptions of existing levels of performance in hospitals and in physicans' offices. Until such empirical data become available, it is unlikely that measurement of physicians' performance can achieve its proper place as both a scientific endeavor and an effective professional mechanism for continuously raising the quality of medical care received by patients.

Discussion

Despite well-documented shortcomings, medical records remain the best source of data on the technical performance of physicians.[48] The literature also makes it clear that under certain conditions the amount of important information entered into the record can be increased substantially (Table 3). One example is the use of printed summaries which remind physicians of pertinent clinical facts concerning their patients.[60,61] Another is the introduction of forms based on protocols or sound empirical studies that specify the type of information needed to determine whether the patient has received proper treatment.[62-64] In all these instances in which special data collecting forms were used, substantial improvement occurred in the technical performance of the physician or surgeon (Table 4). The available evidence strongly suggests that most physicians keep records in a way that may not be in their patients' best interests.

If sustained trends are the most dependable indicators of future events, then it may be safely concluded that external pressures for assuring satisfactory performance by individual physicians will increase through state laws and regulations. These are now in place in California and Michigan. However, the importance of allowing the initiative to remain with the private sector is well recognized, for without this no amount of regulation can improve the technical and personal aspects of care. One major feasibility study based on this principle has been undertaken recently by the American College of Physicians and the American Society of Internal Medicine, in cooperation with the American Hospital Association.[65]

The future of professional self-regulation in providing de facto assurance of quality—that is, in measuring individual physicians' performance—will be determined by three key considerations: the validity and feasibility of the methods, their professional sponsorship, and the motivation provided for individual practitioners. Valid methods now are available for measuring important elements of performance by surgeons, internists, pediatricians and family physicians. With reasonable investment of effort, the scope and practicality of these techniques can be increased substantially.

Methods of measuring performance do not exist in a vacuum. They require sponsorship by professional bodies that can maintain the confidence of both the public and the profession. The work of the National Board of Medical Examiners (NBME) offers a direct analogy in the field of knowledge assessment. NBME has established itself as the foremost organization for devising and administering objective tests reflecting national consensus on the current state of knowledge in basic and clinical aspects of medicine. It does this by virtue of drawing on faculty members and practitioners of recognized stature in their respective basic medical sciences and clinical disciplines. Comprising the test committees, these experts annually review and revise the content of examinations in accord with emerging new knowledge derived from clinical and biomedical research.

Comparable professional auspices are needed

for further development and application of methods for measuring individual physicians' performance, using important indicators of the technical quality of care. This could well begin with designing and conducting valid interhospital comparisons on the basic components of surgical or medical care. National standards for these elements should be set by the respective specialty societies. By this means, hospital boards and medical staffs could dependably determine whether they are performing in accord with contemporary national standards.

The third requirement for improving our capability for measuring physicians' performance is adequate incentive for individual physicians to participate in such activities. At present, continuing medical education (CME) credits are given for attendance at or participation in accredited programs. Under certain circumstances, CME credits are granted for activities that pertain more directly to the assessment of performance. This distorts the fundamental purpose of CME credits, which is to motivate physicians to remain abreast of advances in knowledge.

What is needed is a companion credit to be granted by professional societies to physicians who engage in organized efforts for the primary purpose of evaluating and improving their own performance. This might be termed a "performance assessment credit." The societies would define the characteristics of such organized efforts or actually accredit them, as they now accredit institutions for CME. The combined requirement of a specified number of CME credits and performance assessment credits would provide more direct public assurance that each physician's performance is being examined and improved. The combined program would provide the opportunity for specialty societies to give formal recognition to those members whose learning habits (CME), test scores (recertification examination or its equivalent) and measured performance in the care of patients all correspond to the standards of the particular specialty. If this were done, granting performance assessment credits would serve both as an incentive and reward to physicians to participate in organized efforts to evaluate and improve their own performance.

It is generally assumed that the cost of measuring physicians' performance is prohibitive. However, three important points should be considered. First, and most important, the potency of medical as well as surgical care now is such that costs to patients of inadequate, inappropriate or harmful medical care are great in human as well as in financial terms. Second, many "quality assurance" activities now conducted in hospitals have as their ostensible purpose the assessment of physicians' performance, but actually provide an unspecified sampling of overall patient care. The cost of these efforts would be no greater if they were designed to assess individual physicians' performance. Third, assuming that definitive evaluations of performance would be made every five years or so, the costs figured on an annual basis would be less than the cost to physicians of their present pursuit of CME.

Discovery of variations in the incidence of serious deficiencies in hospital care calls for the application of a balancing test—that is, weighing the possible harm to patients against the possible harm to a physician's professional standing. Because so much of what has been done in evaluating physicians' performance has either had questionable validity or has been conducted as a limited study, the balancing test has not received the attention it deserves in the literature. If in Figures 1 through 3, one selects a score so extremely different from the median or mean so as to be absolutely certain that no medical staff is judged unfairly, then some patients will assuredly continue to receive substandard care. On the other hand, if the standard is applied rigidly at the statistical mean, not enough weight will be given to factors other than technical performance that can and do influence outcomes. The key considerations in arriving at a proper judgment are (1) the reliability of the data, (2) the seriousness of the actual or probable adverse effects on patients and (3) the probability that additional patients will suffer serious adverse effects if performance is not improved.

Conclusion

An organized effort to proceed with measurement of physicians' performance will provide greater protection against further incursions on the profession's autonomy than any other voluntary effort. Developing such programs will show more convincingly than any other action that physicians are fundamentally committed to the welfare of their patients. From the public's perspective, the major benefit will be the protection of patients from substandard care. From the profession's perspective, the effort will more fully realize the common purpose of all current efforts in self-

regulation: progressively improving physicians' performance in relation to continuously upgraded national standards.

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Refer to: Comfort A: Nationalized health care—An American solution (Commentary). West J Med 133:89-90, Jul 1980

Commentary

Nationalized Health Care—An American Solution

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To an expatriate English doctor in America, Dr. Watts's predictions in the October 1979 issue (Nationalized Health Care—A Juggernaut in 1981) carry an overwhelming sense of déjà vu, for most of the same things were said by British Medical Association spokesmen before the British health service and by Canadian doctors before the Saskatchewan health plan. In Britain, Lord Horder tried to organize a strike against the proposals; in Saskatchewan an actual strike took place, ending hurriedly in response to public reaction. In each case a health service emerged; in neither case is it perfect. In both cases the result resembles the Congress, the Supreme Court, the Constitution and the Presidency in the United States—in that democratic citizens grumble about them incessantly, but only a lunatic would want to abolish them.

British doctors (who, contrary to common American belief, are not government employees but practice with virtually complete discretion) are actually subject to far less arbitrary official meddling than their American colleagues, who have to square their prescribing with Food and Drug Administration rules. They probably have marginally less paperwork. I think my American colleagues do have valid reasons for worry about what a future Administration may do, but not for the reason that transfer of the cost of medicine from the patient to taxation revenue—which is what a health service means—need necessarily corrupt the practice of medicine. So can the present method of rationing by price. When Dr. Watts asks what a health service would achieve which is not now being done, the $64,000 answer is "provide the poor, the old and those of moderate means with access to medical care," as well as give doctors the chance to doctor without having to run a business as well. In Europe we do not have to pass the hat to get treatment for a child with leukemia.

The tendency in America is to have the argument both ways; on one hand, to insist on the merits of treating medicine as a marketplace commodity, and on the other, to talk about doctor-patient relationships as a professional trust. A professional is one who earns in order to work; a tradesman works in order to earn. Either sickness is to be an industry, or health care is to be a right—and it is extremely difficult to have it both ways. Doctors have opted irrevocably to be a profession.

Does this mean that I am advising the immediate importation of a European- or Canadian-style health service to the United States, or that I confidently expect to see my capitalistic colleagues dragged kicking and screaming into one, after which they may earn less but will practice better medicine and like it? Actually I am "advising" nothing, because I am not an American voter and it is none of my business. Even if I were not disqualified, alas no. I think worry about the future is not confined to the avaricious and unprincipled minority, and I am beginning to see why. European health services are administered by normally incorruptible and normally competent career administrators applying the law; public service is an honorable career (in Britain, the phrase "Her Majesty's Service" makes the occupation sound as dignified as that of judge). Imagine the identical system run by the General Services Administration, for example, administered through "guidelines," not laws, and geared to provide welfare for those who write guidelines, conduct "preliminary studies," distribute pork barrels and decline to muzzle the ox when he treadeth out the corn, and one can see clearly why Dr. Watts and other responsible colleagues are apprehensive.

One does not need to wrap oneself in the flag to say that an American health service will have to be American, exactly as a Japanese health service will have to be Japanese. Free enterprise (warts and all) has been an undeniable American talent, and public service has not; or rather, public service has been seen (like political office) as a rogue branch of free enterprise. So the answer, if I can presume to suggest it, is to transmute free enterprise out of the wallet-biopsy tradition, and

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stand it fully on its feet under the more responsible guise of mutual aid and direct action—which is precisely what Dr. Watts hints at in his last proposition.

Compassionate physicians who want neither guidelines nor bureaucrats, who object to ukases legitimizing advertising and orders to cooperate with bone-setting quacks, and who already see medicine as a profession and a service, (not ill health as a gold mine)—and for all the huffing and puffing I think they are in a majority—need to move beyond the position of self-defense. These physicians should prepare to do their stint in primary-care medicine rather than wanting to be specialists immediately (in Britain it is the title of specialist which is rationed), and stop talking about leaving the practice of real, house-calling, dirty-boots medicine to "nurse practitioners." They should be getting together with colleagues, patients and advocacy groups to take the ball away from the bureaucracy and to make health care delivery work. The format of such health care may vary greatly: there is room for health maintenance organizations (which closely resemble British health-service group practices), fee-for-service practices, free clinics and many other exemplary experiments on a local level. They exist already.

If at the end of the day there are still no doctors in rural areas and no decent health care in the ghettos, then these same physicians will have failed. If weaker brethren go on talking like the Godfather, they will get an official Mafia imposed on them. But if we address the community, find out what it needs, and go along with those needs, we can reckon on massive public support against "guidelines" and their career fabricators. There is a genuinely popular spirit abroad which tends more and more to recognize that government is the common enemy of humanity. At first flush, not a traditional American view, but very like the view that held that King George's officials were the common enemy of humanity—a view that produced notable and American consequences.

I am suggesting that a valid American solution to the problem of health care may well turn out to be local and populist in emphasis. Though it will need federal subvention in many areas to enable it to cohere, if it has a popular base in the genuine interdependence of medicine and community groups it will represent taxation with representation, an ideal which now exists in name but hardly in practice. At present, the consumers are taxed and the sickness industry, which can support candidates, is represented. Nineteenth century slogans about socialism and capitalism are not particularly helpful. Europe is tending away from them because neither ideology exists anywhere in pure culture. If we wanted a label for local populist initiative it would be "anarchism," which does not mean bomb throwing and subversion, but, rather, the conviction that centralized authority should be reduced to a practical minimum. Medicine, provided it has a social conscience, is a good proving ground for such a theory of society.

When I attend professional meetings in this country I keep quiet, as a noncitizen must. Doctrinaire noises about the merits of the free marketplace are made by a minority (often an official one, for doctrinaires tend to be active in political organizations) while the vast majority of my colleagues listen apprehensively, and the set-piece debates at AMA conferences run hither and thither as sheep having no shepherd. These physicians can read the writing on the wall; like Dr. Watts, they are apprehensive about centralist schemes out of Washington. If someone got up and said "Look, I have a better idea," the pharisees among us might respond "He hath a devil"; however, the common people of medicine probably would hear him gladly. Yet how many would be prepared to engage their patients, and the town meeting in general, in a debate on how health care could be better delivered (starting now), and then begin with colleagues so to deliver it? It is the only way in which both demagogues and racketeers (who exist) can be frustrated. Together with mutual aid and direct action it is also an anarchist principle that in proposing a course of action, the *i*'s should not be dotted and the *t*'s crossed, because the action taken should be mutually devised by the consent of the actors, not prescribed, however disinterestedly. Thomas Jefferson would have approved.

When will the organized profession stop sounding like oil executives whose profits are threatened, and start holding town meetings and listening to what is said at them? If Washington bureaucracy and shenanigans are a uniquely American misfortune, participatory democracy is a uniquely American resource. It could generate an American health care delivery system that is unique in being a genuine health service, rather than an adequate device for the management of sickness.

CLINICAL NOTES IN DIAGNOSTIC CARDIOLOGY

Refer to: Roberts NK, Child JS, Cabeen WR Jr: Congestive cardiac failure in a 20-day-old infant (Clinical Notes in Diagnostic Cardiology). West J Med 133:91-94, Jul 1980

Congestive Cardiac Failure in a 20-Day-Old Infant

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UNLIKE CARDIAC FAILURE in adult patients, in babies this condition generally develops insidiously and with different clinical features. In contrast to an adult, a baby will show physical signs only and will not be able to communicate symptoms. It is important to recognize the more subtle signs of congestive heart failure in an infant and to appreciate the most likely causes, their evaluation and treatment. Characteristically, the baby becomes restless and the respiratory rate increases. The faster respiratory rate does not let the infant maintain his or her feeding rate and, consequently, the feedings become prolonged and frequent. Unlike adult cases, only sacral and pedal edema develop in the infant; fine crepitations in the bases of the lungs usually occur as terminal events. A rapid heart rate, often 200 to 220 beats per minute, is a typical early finding and the baby is generally diaphoretic. Key findings on clinical examination are a gallop rhythm and a prominent liver edge.

At very young ages, cardiac failure is a common manifestation of heart disease. At the time of birth there is already a sudden and considerable increase in cardiac output, and any further demand may result in heart failure.

Causes of heart failure in this age group are congenital cardiac defects, primary myocardial disease and secondary conditions (Table 1).

Report of a Case

Recently, we saw an illustrative case of a baby girl who was born by a normal delivery after a pregnancy of normal duration. On her third day of life, she was discharged from hospital. She was scheduled to be seen at one month of age by her pediatrician. The infant was well until two weeks of age when her mother noticed that she was not hungry. Because she would not take a further feeding and appeared restless that night, her mother took her to the pediatrician the following morning.

The pediatrician noted that the infant's pulse rate was between 250 and 300 beats per minute.

TABLE 1.—*Some Causes of Heart Failure in Newborn Infants*

- Congenital cardiac defects
  - Left-to-right shunts, ventricular septal defect; atrial septal defect, patent ductus arteriosus
  - Right-to-left shunts, hypoplasia of the left ventricle
  - Bidirectional shunts, "d" transposition of the great arteries, truncus arteriosus
  - Obstruction, coarctation of the aorta, pulmonary or aortic stenosis
  - Regurgitation, absent pulmonary valve, aortic insufficiency, mitral and tricuspid insufficiency
- Primary myocardial disorders
  - Ischemia due to coronary artery abnormalities
  - Endocardial fibroelastosis
  - Glycogen storage disease
- Disorders which secondarily affect the myocardium
  - Cardiac arrhythmias
  - Myocarditis
  - Anemia
  - Over transfusion
  - Respiratory distress

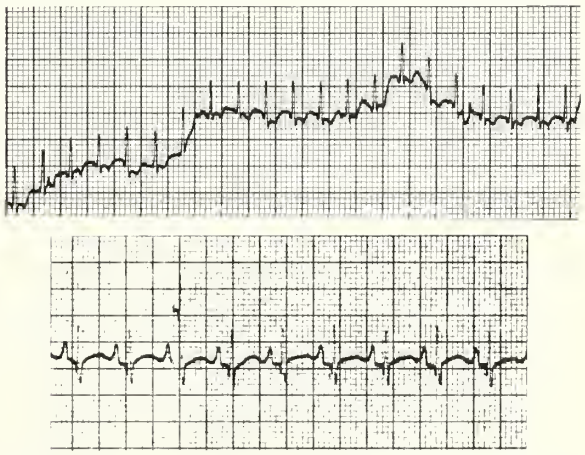

Figure 1.—Top trace, A supraventricular tachycardia with a ventricular response of 295 beats per minute. Lower trace, Immediately following DC cardioversion, sinus rhythm was established at a rate of 155 beats per minute (normal for an infant less than one month old).

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The liver edge was slightly prominent. The arterial pulses were diminished in volume but were present, equal and synchronous. The skin was warm and of normal color. No cardiac murmurs were detected.

The pediatrician referred the baby to the school of medicine at the University of California, Los Angeles (UCLA) because he was concerned that the palpable liver edge was a sign of early hemodynamic decompensation. On arrival in the emergency room, a glance at the baby showed that her condition had deteriorated substantially. Her skin showed blotchy areas and was cold. Her pulse rate was 250 beats per minute and the carotid pulse was thready. An electrocardiogram disclosed a supraventricular tachycardia (Figure 1, top trace). Carotid sinus massage and eyeball pressure were not effective in reducing the ventricular rate and, because it was believed that the rate was inappropriately fast, a synchronized 10 watt-second direct current (DC) shock was given. She reverted to sinus rhythm (Figure 1, lower trace) and within five minutes had become pink and warm in the peripheral areas. At that time a roentgenogram of the chest (Figure 2, left) was taken and the electrocardiogram was repeated. The infant was admitted to hospital and placed on a 24-hour continuous electrocardiographic tape recorder. Therapy with digoxin was begun. Her subsequent hospital course was uneventful and she was discharged after three days. On discharge, an echocardiogram and repeat roentgenogram of the chest (Figure 2, right) showed no abnormalities. Her 24-hour electrocardiogram showed intermittent ventricular preexcitation (Figure 3). Treatment with digoxin was continued, and when she was last seen (at a year of age) she had had no further episodes of tachycardia.

Discussion

Cardiac failure in a newborn infant does not present the classic features of "forward" and "backward" failure that are typical of adults. In fact, sacral edema, pedal edema and fine crepitations in the bases of the lungs are often terminal

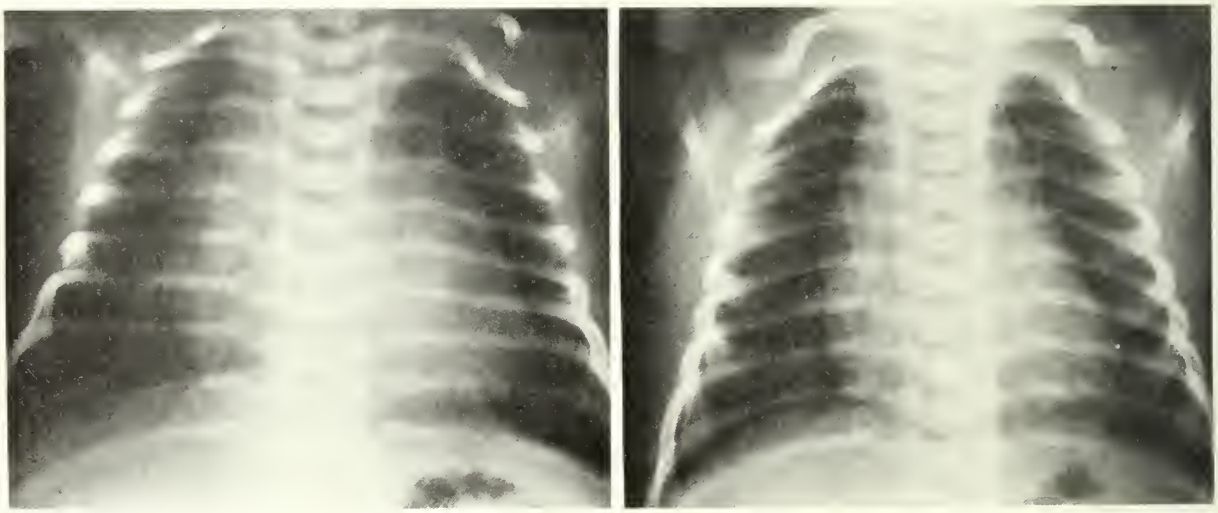

Figure 2.—Left, a roentgenogram of the chest shows a substantially enlarged heart. **Right,** three days later, a repeat x-ray study of chest shows that the heart has returned to a normal size.

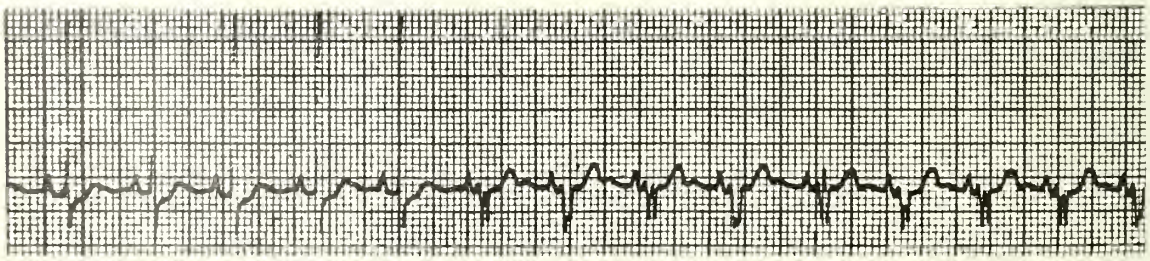

Figure 3.—A representative electrocardiographic rhythm strip initially shows five normal complexes. Although the P wave has not changed for the sixth complex, the PR interval is shortened and there is a slurred QRS complex diagnostic of intermittent ventricular preexcitation (Wolff-Parkinson-White syndrome).

findings in neonatal congestive heart failure. In our patient, neonatal heart failure presented with clinical features of a loss of appetite, restlessness and sweating. A baby, unlike an adult with cardiac failure, is usually tachypneic, has a tachycardia and a prominent liver edge.[1] In our case, when the pediatrician examined the baby, it was obvious that she was in borderline cardiac failure. The pediatrician knew that once there was hemodynamic decompensation, there would be tissue hypoxia and acidosis which would lead rapidly to substantial clinical deterioration and, possibly, to death. He had two concerns—diagnosis and treatment. Typically, a neonate can withstand a supraventricular tachycardia with a ventricular response of between 250 and 300 beats a minute for about 24 hours, and only subsequently is there deterioration. However, once there is clinical evidence of cardiac decompensation it is not long before shock develops. Because the baby was clearly in shock by the time she arrived at UCLA, and because her heart rate was inappropriately rapid, we decided to use a synchronized DC cardioversion. For small children, 2 watt-seconds per kg of body weight is given with 10 watt-seconds being the minimum effective energy level.[2]

Rapid improvement is the rule following restoration of sinus rhythm, provided that there is no underlying cardiac defect. Because the baby responded so well to cardioversion and had no abnormal physical cardiac signs, we concluded that if there was underlying congenital heart disease, it was subtle. Infants with hypoplastic syndromes of the left ventricle (aortic atresia) have a typical presentation; they are well at birth, then on the second day progressively more severe cardiac failure develops and, finally, they invariably die on the third day. Those with "d" transposition of the great arteries are cyanotic, and the cyanosis is generally greater in those without septal defects. Infants with a coarctation of the aorta present with a variety of signs ranging from differential cyanosis to absent femoral arterial pulses. An infant with a large ductus arteriosus who presents in cardiac failure has a characteristic murmur.

Generally, signs of myocardial disease are reflected on an electrocardiogram. High-voltage QRS complexes in the precordial leads are characteristic of endocardial fibroelastosis. Low-voltage QRS complexes and T wave abnormalities may be found in infants with a myocarditis, but may also be found in infants with a persistent tachyarrhythmia. A type of glycogen storage disease (Pompe disease, type II) is associated with conditions other than heart failure in infancy; however, the electrocardiogram generally shows a short PR interval. The presence of an arteriovenous fistula may be indicated by a cerebral bruit. About 24 hours after DC cardioversion, it is important to look specifically for more subtle congenital heart lesions such as the Ebstein anomaly of the tricuspid valve, "L" transposition of the great arteries or a prolapse of the mitral valve.[3] In our patient a physical examination, electrocardiogram, echocardiogram and roentgenogram of the chest showed no abnormalities. Therefore, we determined that the episode of cardiac failure was probably related to ventricular tachycardia.

The mechanism for such an arrhythmia varies from case to case, and both reentrant and automatic foci have been documented. Sinus node, right and left atria, atrioventricular node and His bundle sites are also found as are accessory pathways. The latter site for a reentry tachycardia has been incriminated in 80 percent of such events at this age.[4]

A 24-hour electrocardiographic recording is essential once the arrhythmia has been stopped. One can attempt to record either the precipitating or terminating events or even the intermittent periods of accessory pathway conduction. In our case, intermittent shortening of the PR interval and the appearance of a delta wave were found (Figure 3).

To manage such episodes of supraventricular tachycardia there are three basic avenues of treatment: (1) Reduce the precipitating cause which is often a premature atrial or ventricular contraction, (2) cause the rapid supraventricular arrhythmia to be conducted only at a slower, controlled ventricular rate, or (3) enhance measures to terminate the tachycardias.

The most practical measure is still to decrease the rate of atrioventricular nodal conduction with digoxin therapy. Over 90 percent of infants under 4 months of age who present with supraventricular tachycardias respond favorably to digoxin, and by 6 months of age do not have any further arrhythmias.[5] Theoretically, treatment with digoxin in patients with accessory pathways may be hazardous. Not only does digoxin slow conduction down the antegrade pathway through the

atrioventricular node, but it enhances conduction through the lateral accessory muscle connections (Kent bundles) and, thus, may theoretically speed up a reentrant tachycardia. However, digoxin may be safely administered to infants because their accessory pathways are usually perinodal, with response properties to digoxin more like atrioventricular node than atrial muscle. In adults, digoxin therapy is particularly hazardous if atrial fibrillation occurs because there may be a very rapid ventricular response. In most infants under 4 months of age, the disease is self-limiting because the accessory atrioventricular nodal fibers are probably fetal remnants which fail to act as alternative conduction pathways as the heart matures.

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Increased Incidence of Diabetes

Diabetes is increasing at an alarming rate. It is estimated by the National Commission on Diabetes that diabetes is increasing at a rate of about 6 percent per year. The progression may seem familiar in this time of economic turmoil, when we think about interest rates and compounded rates of interest. Within 12 to 15 years the incidence of diabetes will double in this country. Within 25 years the incidence will quadruple.

We are dealing with a very major public health problem. In an American born today there is a one in five chance of diabetes developing in his lifetime. Diabetes is the third leading cause of death in this country, taking approximately 300,000 lives a year. A diabetic patient is 17 times more prone to kidney disease, 5 times more prone to gangrene (which often leads to amputation), and twice as likely to have a heart attack or stroke than a person without diabetes. This disorder decreases life expectancy by a third. And the economic toll of the disease in the United States today, excluding complications of diabetes, is approximately $5.3 billion annually.

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Information

Refer to: Gerber A: Improved quality of life following a Kock continent ileostomy (Information). West J Med 133: 95-96, Jul 1980

Improved Quality of Life Following a Kock Continent Ileostomy

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THE TIME-HONORED TEACHING of physicians has been "to treat the patient and not just the disease" by taking into account emotional as well as physical problems. A new *holistic* school of medicine would expand this traditional role of physicians to include areas usually the domain of cultural anthropologists, ecologists, economists, sociologists and the clergy. Although their approach may differ, both the old and new medical philosophies share the common goal of not only getting patients well, but of improving the quality of their lives.

The development of the continent ileostomy over the past decade by Nils Kock of Sweden is a magnificent example of achieving this goal. Rarely has a surgical breakthrough resulted in so dramatic an improvement in patients' life-styles.

There was plenty of room for improvement. For despite the important advances of Brooke[1] and Turnbull[2] in surgical technique, and the greater efficiency of the newer external appliances, a conventional ileostomy is far from ideal. Local skin irritation due to leakage or allergy to the adhesives is common, and in some 10 percent of patients who have had ileostomies another operation is necessary because of prolapse, retraction, stenosis or peristomal hernia.[3] The concern of this paper, however, is not with the local complications of a conventional ileostomy, but with the appreciable number of unhappy patients who are psychologically, socially or sexually maladjusted due to the constant wearing of a bag filled with liquid intestinal contents.

The Kock continent ileostomy resolves almost all of these problems by eliminating both a protruding stoma and an external appliance.[4] This operation creates an internal reservoir for storage and a nipple valve to maintain continence (Figure 1). The reservoir is quickly and easily emptied two or three times a day by means of a catheter.

The operation has been slow to gain acceptance because of numerous complications during its evolutionary period.[5-7] The most disconcerting of these has been slippage of the nipple valve with a resultant loss of continence. Leakage under these circumstances is particularly distressing because the continent ileostomy stoma is flush with the skin and placed low on the abdomen. Nipple valve problems have been largely resolved, however, by a series of innovative changes in operative technique,[4,8,9] and continence is now almost always assured.

From October 1977 to October 1979, continent ileostomies were constructed in 29 patients with no mortality and minimum morbidity. The patients ranged in age from 17 to 66, with a median of 34 years. The original diseases necessitating a proctocolectomy and ileostomy in these patients were ulcerative colitis in 25, multiple polyposis in 2 and necrotizing amebiasis in 2. Of these operations, 22 were conversions of conventional ileostomies, either because of stomal problems or for psychological reasons. The remainder were combined with proctocolectomy.

There were no major postoperative complications. In two patients minor wound infections developed, and in one a pelvic abscess occurred. The pelvic abscess, in a patient receiving high-dose steroids while undergoing proctocolectomy, drained spontaneously through the perineal wound. Gastrointestinal decompression was not used routinely following operation.

Late complications arising 3 to 12 months following the procedure, required reoperation in five patients. Two pinpoint fistulas due to silk sutures were easily closed, one without entering the peritoneal cavity. A third fistula, in a patient who probably has Crohn disease* but who mistakenly was operated on after a diagnosis of ulcerative colitis, has recurred after surgical closure. A second operation was necessary in one patient who had occasional incontinence because of slippage of the nipple valve. Finally, a minor operation to correct a recurrent everting nipple valve,

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*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

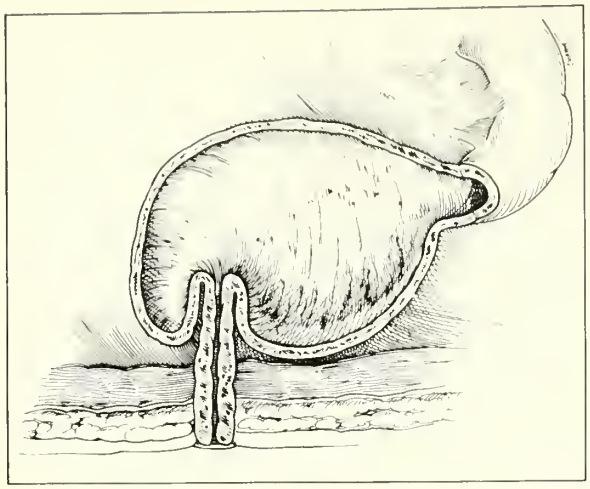

Figure 1.—Drawing of a Kock reservoir ileostomy with nipple valve.

reducible by the patient, was only partially successful.

The overall results have been excellent: no patient has required the wearing of a bag following the initial operation. Moreover, the late complications listed above should pose less of a problem in the future because of modifications in the operative technique.

Chronic ulcerative colitis is a disabling disease for which medical treatment is only supportive as the cause is unknown. Patients may have 15 to 20 bloody, diarrheal stools per day, leading to obvious changes in their life-style. Anemia and weakness are common, and fulminating acute attacks may be life-threatening. In long-standing cases, there is an increased risk of carcinoma of the colon. The only definite cure is proctocolectomy, but, in the past, procrastination has been the rule because patients have been understandably loath to wear an external bag filled with intestinal discharge for the rest of their lives.

For these patients the Kock ileostomy offers an attractive alternative to the chronic disability, so that an aggressive surgical approach holds definite advantages over the conservative management of the past. No longer does an ileostomy need to be considered a last-resort or emergency operation, and earlier surgical intervention is certain to lower the mortality and morbidity of proctocolectomy.

A continent ileostomy is also frequently indicated in a second category of patients: those who have had a proctocolectomy and conventional ileostomy but who are having stomal complications or who are unable to adjust psychologically to an external appliance. For these patients, revision to a continent ileostomy is a most gratifying procedure.

A continent ileostomy can also be carried out for other uncommon diseases requiring proctocolectomy, but the Kock procedure is usually contraindicated in Crohn disease because of the high recurrence rate in the small intestine.[4]

The 22 patients in this series whose conventional ileostomies were converted to continent ileostomies were closely questioned regarding changes in their life-style. Each of them has noted a significant and often dramatic change for the better in the quality of his or her life. Skin problems and odor have been eliminated; time spent in care of the ileostomy has been considerably shortened; clothing is worn more comfortably; confidence has increased during athletic endeavors and on social occasions, and sexual relations have improved considerably.

Finally, the monetary savings to a patient with a continent ileostomy is substantial. In contrast to a patient with a conventional ileostomy whose outlay is $500 to $800 a year for external appliances, a patient with a continent ileostomy spends only $5 for a new catheter every six months.

Summary

A conventional ileostomy is no longer the last-resort, unsatisfactory operation of the past because of advances in surgical techniques and in preoperative and postoperative care, as well as improvements in modern external appliances. A continent ileostomy, however, substitutes an unobtrusive gauze pad for a bag filled with liquid intestinal contents. The advantages are obvious. There are few operations that contribute so dramatically to an improved quality of life as a Kock continent ileostomy.

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Information

Loan Fund for California Medical Students

At its 1980 Annual Meeting, the California Medical Association (CMA) House of Delegates unanimously adopted Resolution 901-80 which requested the California Medical Education and Research Foundation (CMERF), a nonprofit, tax-exempt, subsidiary of the California Medical Association, to establish a self-renewing, low-interest student loan fund by asking CMA members to contribute $100 a year for three years and to invite them to make additional periodic voluntary contributions.

This action by the House of Delegates recognizes the necessity to assist needy students who are faced with high interest rates even if they are able to secure loans which have become increasingly difficult to obtain.

Voluntary contributions, which are tax-deductible, will enable CMERF to start developing a fund which can be used to provide loan guarantees. The initiation of such a fund will necessarily depend upon the response of every California physician. It is possible to help assure the future of the practice of medicine by helping support future physicians. Contributions for the medical student loan fund may be made to the California Medical Education and Research Foundation, 731 Market Street, San Francisco, CA 94103.

Are You an Artist?

Are you an artist as well as a physician? If so, there is an annual art exhibit of national caliber strictly for doctors who are artists. The sponsoring organization is the American Physician's Art Association, now in its 43rd year. It meets annually with the Southern Medical Association and presents its yearly exhibit in conjunction with the SMA meeting. The APAA has nearly 500 members across the country.

In 1980 the SMA will meet in San Antonio, Texas, from November 16 through 19. All physicians who work in the fields of painting, sculpture, photography, graphic arts, design and creative crafts are encouraged to join the APAA to submit entries for the November exhibit.

Membership is open to all physicians. Southern Medical Association membership is not required. Those interested should write to

Milton S. Good, MD, Treasurer, APAA
610 Highlawn Avenue
Elizabethtown, PA 17022

in memoriam

California Medical Association

BELT, ELMER, Los Angeles. Died May 17, 1980 in Los Angeles of cerebrovascular accident, aged 87. Graduate of the University of California Medical School, Berkeley-San Francisco, 1920. Licensed in California in 1920. Dr. Belt was a member of the Los Angeles County Medical Association.

CARDEY, PAUL C., Cypress. Died October 30, 1979, aged 72. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1948. Licensed in California in 1948. Dr. Cardey was a member of the Los Angeles County Medical Association.

CAREY, Wells C., College Place, Washington. Died in August 1979 in College Place, aged 71. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1945. Licensed in California in 1946. Dr. Carey was a retired member of the Humboldt-Del Norte County Medical Society.

ESCAMILLA, ROBERTO F., San Francisco. Died May 23, 1980 in San Francisco, aged 74. Graduate of Harvard Medical School, Boston, 1931. Licensed in California in 1933. Dr. Escamilla was a member of the San Francisco Medical Society.

FENTON, MELVILLE, San Bernardino. Died May 18, 1980 in San Bernardino, aged 78. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1926. Licensed in California in 1926. MD degree from California College of Medicine, 1962. Dr. Fenton was a member of the San Bernardino County Medical Society.

HELLER, ROBERT A., Long Beach. Died July 1, 1979, aged 77. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1946. Licensed in California in 1946. MD degree from California College of Medicine, 1962. Dr. Heller was a member of the Los Angeles County Medical Association.

LELAND, SHERMAN, San Francisco. Died May 31, 1980 in San Francisco, aged 77. Graduate of the Creighton University School of Medicine, Omaha, 1930. Licensed in California in 1930. Dr. Leland was a member of the San Francisco Medical Society.

LORDAN, JOHN P., Beverly Hills. Died November 9, 1979, aged 79. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1927. Licensed in California in 1929. Dr. Lordan was a member of the Los Angeles County Medical Association.

PRINS, LEO R., JR., San Leandro. Died April 23, 1980, aged 70. Graduate of the University of Minnesota Medical School, Minneapolis, 1933. Licensed in California in 1951. Dr. Prins was a retired member of the Alameda-Contra Costa Medical Association.

REA, BERNARD J., Sacramento. Died April 5, 1980 in Sacramento, aged 93. Graduate of Western Reserve University School of Medicine, Cleveland, 1919. Licensed in California in 1919. Dr. Rea was a retired member of the Sacramento-El Dorado Medical Society.

SCHWARTZ, ERMINIA E., Los Angeles. Died May 24, 1979, aged 85. Graduate of the College of Physicians and Surgeons of San Francisco, 1917. Licensed in California in 1917. Dr. Schwartz was a member of the Los Angeles County Medical Association.

SHELBY, DONALD C., Los Angeles. Died April 5, 1980, aged 78. Graduate of the State University of Iowa College of Medicine, Iowa City, 1925. Licensed in California in 1928. Dr. Shelby was an associate member of the Los Angeles County Medical Association.

WALTON, HAROLD M., Loma Linda. Died in April 1980, aged 88. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1928. Licensed in California in 1928. Dr. Walton was a retired member of the San Bernardino County Medical Society.

WILLARDSON, DONALD G., Long Beach. Died May 7, 1980, aged 53. Graduate of the University of Utah College of Medicine, Salt Lake City, 1955. Licensed in California in 1956. Dr. Willardson was a member of the Los Angeles County Medical Association.

WIMALARATNE, KITHSIRI N., Madera. Drowned in Madera on May 31, 1980, aged 39. Graduate of the Faculty of Medicine, University of Ceylon, Colombo, 1967. Licensed in California in 1976. Dr. Wimalaratne was a member of the Fresno-Madera Medical Society.

Washington State Medical Association

BIDDLE, ARTHUR S., Seattle. Died May 20, 1980, aged 53. Graduate of Northwestern University Medical School, Chicago, 1952. Licensed in Washington in 1958. Dr. Biddle was a member of the King County Medical Society.

HICKS, WILLIAM W., Ellensburg. Died May 2, 1980, aged 84. Graduate of the University of Virginia School of Medicine, Charlottesville, 1920. Licensed in Washington in 1930. Dr. Hicks was a member of the Kittitas County Medical Society.

NORTHROP, CEDRIC, Seattle. Died April 30, 1980, aged 74. Graduate of the University of Oregon Medical School, Portland, 1936. Licensed in Washington in 1942. Dr. Northrop was a member of the King County Medical Society.

VANNEMAN, JOHN W., Seattle. Died May 2, 1980, aged 61. Graduate of the Chicago College of Osteopathy, 1945. Licensed in Washington in 1946. Dr. Vanneman was a member of the King County Medical Society.

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HELP! Community Family Clinic in East Los Angeles desperately needs tax deductible, medical and lab equipment, pharmaceuticals. Joe Fae/Robert Lange, MD, La Clinica Familiar del Barrio, 133 N. Sunol Dr., East Los Angeles, CA 90063.

FAMILY PRACTICE—PALM SPRINGS, CALIF. Associate needed for dynamic solo practice in magnificent Palm Springs. Must be Bd. Cert. or eligible. Send CV to Dr. Carl Salzman, MD, Inc., 39000 Bob Hope Drive, Kewit Bldg. Suite 401, Rancho Mirage, CA 92270. (714) 346-5559.

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(Continued on Page 19)

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(Continued on Page 20)

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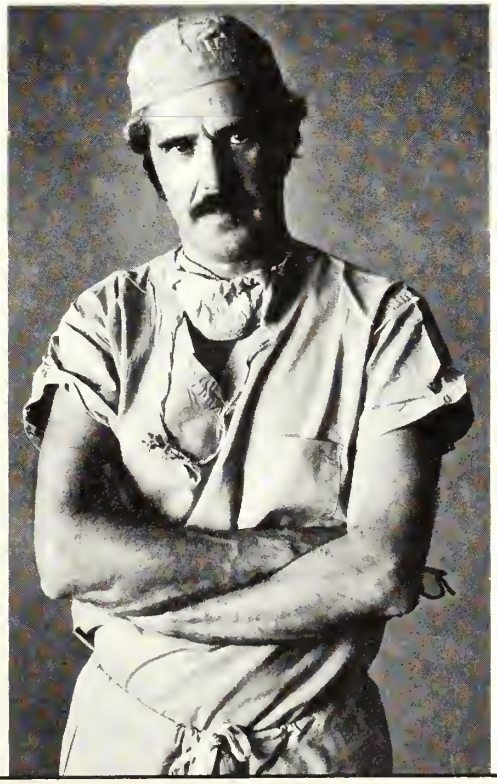

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ANESTHESIOLOGY

October 3-5—**Anesthesia Specialties.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Friday-Sunday. 10½ hrs. $90, AEF member; $165, nonmember. Contact: Walter H. Comer, MD, AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

October 26-28—**Anesthesia and Cardiopulmonary Disease.** Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Sunday-Tuesday. 11 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

November 8-9—**American Society of Anesthesiologists—Refresher Course.** Hilton, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

December 12-14—**Anesthesia: Before and After.** Tucson Hospitals Medical Education Program at Canyon Hotel, Palm Springs. Friday-Sunday. $150. Contact: James P. Angiulo, MD, Kino Community Hosp., 2800 E. Ajo Way, Tucson, AZ 85713.

CANCER

September 6-7—**2nd Annual Preventive Oncology: Nutrition and Cancer.** UCSF and No. Calif. Cancer Program. Saturday-Sunday. $130. Contact: UCSF, Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

October 9-11—**American Cancer Society.** Hilton, Los Angeles. Thursday-Saturday. Contact: N. G. Bolliglieri, MD, ACS, 777 Third Ave., New York 10017.

October 24-26—**Enzymes and Related Proteins in the Diagnosis and Prognosis of Neoplastic Diseases.** UCSD at Vacation Village, San Diego. Friday-Sunday.

October 27-29—**4th Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. 22 hrs. $300. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

Noember 6-8—**Current Concepts in Cancer Diagnosis.** UCLA. Thursday-Saturday.

November 7-8—**Cancer Prevention and Screening.** Claire Zellerbach Saroni Tumor Institute of Mt. Zion Hospital and Medical Center at Holiday Inn on Union Square, San Francisco. Friday-Saturday. 10 hrs. $125 before September 15; $150 thereafter. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

EMERGENCY MEDICINE

July 21-25—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

July 25-27—**Advanced Cardiac Life Support Provider, Recertification and Instructor Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Education Dept., 2310 Mason St., San Francisco 94133. (415) 956-5900.

August 11-15—**Postgraduate Institute for Emergency Physicians, Symposium I:** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

August 25-29—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

September 18—**Abdominal Trauma.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 3-4—**Postgraduate Institute on Emergency Medicine—5th Annual.** UCLA at Miramar-Hilton, Santa Monica. Friday-Saturday. 14 hrs. $170.

October 9-February 5—**Management of Pre-Hospital Emergencies.** UCLA. 5 Thursday evenings.

October 13-17—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $350.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717. (714) 833-5414, Fee and Information office or (714) 833-5526, 5542, Continuing Education in Health Sciences.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

October 16—**Dermatology in the Emergency Department.** UCSD. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 20-31—**Intensive Review of Emergency Medicine.** USC. Two weeks.

November 20—**Clinical Pharmacology in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

December 8-12—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

July 29-August 1—**5th Annual Postgraduate Course and Workshop in Medical Mycology-Dermatomycology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Friday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 2—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

August 7-9—**Society for Pediatric Dermatology—5th Annual Meeting.** SPD and STAN at Doubletree Inn, Monterey. Thursday-Saturday. 15 hrs. $150, members; $200, nonmembers. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

August 8-9—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 15 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

August 13—**Calcium Metabolism—Its Diagnosis and Management.** LLU. Wednesday. 4 hrs. $30.

August 14-16—**A Pan-Pacific Conference on Tuberculosis in the 80s.** Hawaii Thoracic Society, Am. Lung Assn. of Hawaii, Hawaii Dept. of Health and Univ. of Hawaii at Ala Moana Hotel, Honolulu. Thursday-Saturday. $35. Contact: Hawaii Thoracic Society, 245 N. Kukui St., Honolulu 96817.

August 15-17—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

August 15-20—**Neuropsychiatric Issues in the Law, Education and Medicine.** See Psychiatry, August 15-20.

September 5—**13th Annual Symposium on Kidney Disease—Endocrine and Metabolic Functions of the Kidney.** Kidney Foundation of Northern Calif. at Fairchild Auditorium, Stanford Univ. Sch. of Med., Stanford. Friday. 6 hrs. $45. Contact: William Arnopp, Exec. Dir., KFNC, 100 S. Ellsworth Ave., Ste. 305, San Mateo 94401. (415) 347-6646.

September 10—**Hematuria—An Approach to Diagnosis and Therapy.** LLU. Wednesday. 4 hrs. $30.

September 10—**Sexually Transmitted Hepatitis: The Facts of Life.** DREW at Pacific Design Center, West Hollywood. Wednesday. 6 hrs. $25. Write: DREW or telephone: Loren Senseman, (213) 974-7275.

September 15-17—**3rd Annual Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Monday-Wednesday. 20 hrs. $200.

September 17-18—**48th Annual Fall Symposium and 13th Annual George C. Griffith Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Wednesday-Thursday. 13 hrs. $100, member of any heart assn.; $125, nonmember. Contact: Mary Frances Flynn, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231, ext. 59.

September 18-19—**Hypertension.** UCD at Sahara, Lake Tahoe. Thursday-Friday. 15 hrs.

September 25-26—**Annual Physicians' Symposium.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Kari Olila, AHA, 421 Powell St., San Francisco 94102. (415) 433-2273.

September 25-28—**American Society of Ophthalmologic and Otolaryngologic Allergy—Annual Meeting.** Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: William King, MD, 1415 3rd St., Corpus Christi, TX 78404.

September 26-27—**American Society of Internal Medicine.** Islandia Hyatt, San Diego. Friday-Saturday. Contact: ASIM, 2550 M St. NW, Suite 620, Washington, DC 20037.

September 26-27—**Dermatology for the Primary Care Physician.** UCD at Holiday Inn, Napa Valley. Friday-Saturday. 11½ hrs.

September 26-28—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Hyatt on Union Square, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

September 27—**Management of Common Lung Problems.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 6½ hours. $35.

October 1-December 17—**Cardiology.** UCLA. Wednesday evenings.

October 4-11—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

October 8—**Endocrine Review.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. Contact: Janie Sternal, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

October 8—**Modern Therapy for Common Dermatologic Problems.** LLU. Wednesday. 4 hrs. $30.

October 10-12—**Chest Disease Symposium.** The Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

Ocober 13-17—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs. $290.

October 18-25—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $325.

October 23-28—**Pacific Dermatologic Association.** Hilton Riviera, Palm Springs. Thursday-Tuesday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno, NV 89509. (702) 323-2461.

October 27-30—**Practical Electrocardiography Course for Primary Physicians.** Memorial Hospital Medical Center-UCI Center for Health Education at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: Center for Health Education. 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 30-November 1—**Cardiology Update 1980.** American College of Cardiology at Del Monte Hyatt, Monterey. Thursday-Saturday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 30-November 2—**California Society of Internal Medicine—Annual Meeting.** Doubletree Inn, Monterey. Thursday-Sunday. Contact: Carol Parlette, Exec. Dir., CSIM, 703 Market St., 1412 Central Tower, San Francisco 94103. (415) 362-1548.

November 1—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

November 5-8—**American Thyroid Association.** Holiday Inn at the Embarcadero, San Diego. Wednesday-Saturday. Contact: Dorothy Hickler, Exec. Sec., ATA, Univ. of MA Medical Ctr., 55 Lake Ave. N., Worcester, MA 01605. (617) 856-3115.

November 12—**Peptic Ulcer—Its Diagnosis and Treatment in the 1980's.** LLU. Wednesday. 4 hrs. $30.

November 13-15—**Pediatric Allergy and Immunology.** See Pediatrics, November 13-15.

November 17-19—**International Symposium on Status Epilepticus.** UCLA at Miramar-Sheraton, Santa Monica. Monday-Wednesday. 20 hrs.

November 19-21—**Pediatric Cardiology.** USC at Palm Springs. Wednesday-Friday.

November 29-December 1—**Advances in Heart Disease 1981.** American College of Cardiology at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 1-3—**Cardiovascular-Pulmonary Update for the Practicing Physician.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 19 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

December 5—**Recognition and Management of Bleeding Disorders.** Children's Hospital Medical Center of Northern Calif. at Sir Francis Drake Hotel, San Francisco. Friday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

December 5-7—**Cardiac Rehabilitation.** International Medical Education Corp. at Wilshire Hyatt, Los Angeles. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

December 6-7—**Neurology for the Primary Care Physician.** UCLA. Saturday-Sunday.

December 10—**Collagen Disease—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $30.

OBSTETRICS AND GYNECOLOGY

August 9-15—**Reproductive Endocrinology, Infertility and Contraception.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

August 23-28—**Practical Management of the Infertile Couple.** See Of Interest To All, August 23-28.

September 12-13—**Environmental Hazards During Pregnancy: A Clear and Present Danger.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs. $95.

September 25-27—**Advances in Obstetrics.** UCSF. Thursday-Saturday.

November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** UCSD at Bahia Hotel, San Diego. Wednesday-Friday. 20 hrs. $185. Contact: Ronald W. Coen, MD, UCSD Sch. of Med., C-019, La Jolla 92093. (714) 452-4424.

December 5-7—**5th Annual Symposium on Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort. Friday-Sunday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

PEDIATRICS

August 2—**Pediatric Dermatology.** See Medicine, August 2.

September 18-20—**Pediatric Urology.** UCD at Holiday Inn, Napa Valley. Thursday-Saturday. 12 hrs.

October 3-4—**Pediatric Topics: Neonatology.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs. $85.

October 8-9—**37th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: L.A. Pediatric Soc., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

October 25—**Hearing Impaired Child.** Peninsula Hospital, Burlingame. Saturday. Contact: Susan Norrell, c/o Radiology Dept., Peninsula Hosp., 1783 El Camino Real, Burlingame 94010. (415) 697-4061, ext. 479.

October 25-November 1—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education and L.A. Pediatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $200. Contact: Center for Health Education, MHMC, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 27-31—**4th Annual Pediatrics for the Practitioner—A Pediatric Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday. 21 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 1—**Pediatric Dermatology Seminar.** See Medicine, November 1.

November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** See Obstetrics-Gynecology, November 5-7.

November 13-15—**Pediatric Allergy and Immunology.** UCSF. Thursday-Saturday.

November 19-21—**Pediatric Cardiology.** See Medicine, November 19-21.

December 5-7—**Children and Their Skeletons: A Practical Approach.** UCD at Hyatt Del Monte, Monterey. Friday-Sunday.

PSYCHIATRY

August 1-3—**Child Psychiatry.** UCD at Holiday Inn-on-the-Beach, Monterey. Friday-Sunday.

August 15-20—**Neuropsychiatric Issues in the Law, Education and Medicine.** So. Calif. Neuropsychiatric Institute and Am. Psychiatric Assn. at Mauna Kea Beach Hotel, Kamuela, Hawaii. Friday-Wednesday. 14 hrs. Contact: Gail Waldron, MD, SCNPI, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

October 25—**Cognitive Prospectives in Psychiatry.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 14-16—**Infant Psychiatry III: Pathological Infants and Their Parents; Pathological Parents and Their Infants.** UCSF. Friday-Sunday.

November 17-21—**Group Therapy.** UCSF. Monday-Friday.

RADIOLOGY AND PATHOLOGY

July 25-27—**Ultrasound Seminar.** American College of Radiology at San Francisco. Friday-Sunday. 15 hrs. $275. Contact: ACR, 20 N. Wacker Dr., Chicago 60606.

August 2-3—**Self-Assessment Workshop in Dermatopathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday-Sunday. 14 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 9-16—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

September 15-17—**3rd Annual Postgraduate Course in Medical Mycology (Dermatomycology).** See Medicine, September 15-17.

September 27-October 4—**Diagnostic Radiology.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

October 10-12—**Society of Nuclear Medicine—5th Annual Western Regional Meeting.** Airport Marriott, Los Angeles. Friday-Sunday. Contact: SNM, P.O. Box 40279, San Francisco 94140. (415) 647-5909.

October 24-26—**Advances in Immunopathology.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Friday-Sunday. 17 hrs. $120. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

October 28-30—**Gram Negative Organisms: An Approach to Identification.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Thursday. 21 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 13-14—**Using the Clinical Lab.** UCLA. Saturday-Sunday.

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SURGERY

July 28-30—**Primary Care of Hand Injuries and Workshop on Hand Splints and Dressings.** American Society for Surgery of the Hand at Doubletree Inn, Monterey. Monday-Wednesday. 16 hrs. $250. Contact: Am. Soc. for Surgery of the Hand, 2600 S. Parker Rd., Ste. 132, Aurora, CO 80014. (303) 755-4588.

September 2-5—**IV International Symposium on Facial Nerve Surgery.** Ear Research Institute, Los Angeles. Tuesday-Friday. Contact: Facial Nerve Symposium, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

September 10—**Hematuria—An Approach to Diagnosis and Therapy.** LLU. Wednesday. 4 hrs. $30.

September 13-20—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 18-20—**Pediatric Urology.** See Pediatrics, September 18-20.

September 19-20—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

September 25-28—**Cost Effective Urological Diagnosis and Treatment.** Western Section, Am. Urological Assn. and AUA at Marriott's Rancho Las Palmas Resort, Palm Springs. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

September 26-27—**Vitrectomy.** UCSD at Vacation Village, San Diego. Friday-Saturday.

September 28-October 2—**American Academy of Otolaryngology.** Convention Center, Anaheim. Sunday-Thursday. Contact: AAO, 15 Second St. SW, Rochester, MN 55901.

October 3-5—**State of the Art: Recent Advances in Head and Neck Surgery.** Institute for Medical Education and Research at Islandia Hyatt, San Diego. Friday-Sunday. 14 hrs. $200. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126 or (714) 294-5910.

October 9-11—**New Techniques in Hip Resurfacing and Replacement—In-depth Course and Workshop.** UCLA. Thursday-Saturday.

October 25-November 1—**Operative Arthroscopy.** UCLA at Maui, Hawaii. One week.

November 14-15—**Vitrectomy/Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs. $450.

December 3-4—**Controversies and Update in Coronary Artery Bypass Surgery.** White Memorial Medical Center and LLU at Hilton, Los Angeles. Wednesday-Thursday. Contact: Dir. of Cont. Med. Ed., White Memorial Med Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000, ext 1460.

December 11-13—**Trauma.** No. Calif. Chap. of the Committee on Trauma of Am. College of Surgeons at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. Contact: Donald D. Trunkey, MD, Chief of Surgery, S.F. Gen. Hosp., 1001 Potrero Ave., San Francisco 94110.

December 12-13—**Ophthalmology Update.** UCD, UCSF, PMC, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

OF INTEREST TO ALL PHYSICIANS

July 25-26—**Symposium on Fundamentals of Occupational Medicine for Physicians.** UCI at Marriott, Newport Beach. Friday-Saturday. 13 hrs. Contact: Joan Brown, Calif. So. Ctr. for Occupational Health and Safety, UCI, College of Medicine, Community and Environmental Med., Irvine 92717. (714) 833-7241.

August 4-9—**Third Annual Gerontology Institute—Session II.** San Jose State Univ., San Jose. Monday-Saturday. Contact: Office of Cont. Ed., San Jose State Univ., San Jose 95192. (408) 277-2182.

August 10-14—**Western Hemisphere Nutrition Congress VI.** American Medical Association, American Institute of Nutrition, Nutrition Society of Canada, at Biltmore Hotel, Los Angeles. Sunday-Thursday. Contact: AMA, Dept. of Foods and Nutrition, 535 N. Dearborn St., Chicago 60610.

August 14-17—**Sexuality.** Orange County and American Urological Associations at Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

August 16-17—**Parenteral and Enteral Nutrition—A Practitioner's Approach.** Memorial Hospital Medical Center, Long Beach. Saturday-Sunday. 10 hrs. Contact: Clinical Nutrition Dept., Memorial Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801 (213) 595-2231.

August 16-27—**23rd Annual Hawaii Refresher Course.** USC at Sheraton-Waikiki Hotel, Maui. 12 days. 39 hrs. $350.

August 17-18—**Computers in Medicine—Applications of Artificial Intelligence Techniques.** STAN. Sunday-Monday. 11½ hrs. $40. Contact: William J. Clancey, AIM Tutorial Coordinator, Rm. TC 117, Div. of Gen. Int. Med., Stanford Univ. Sch. of Med., Stanford 94305.

August 17-22—**Advanced Diving Medicine.** UCSF. Sunday-Friday.

August 23-28—**Practical Management of the Infertile Couple—4th Annual Edward Tyler Symposium.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. Saturday-Thursday. 16 hrs. $225. Contact: Jetset Tours, 2029 Century Park East, Suite 2130, Los Angeles 90067.

August 24-29—**Family Practice Refresher Course—8th Annual.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

September 6—**Drug Abuse.** UCLA. Saturday.

September 10—**Sexually Transmitted Hepatitis: The Facts of Life.** See Medicine, September 10.

September 22-26—**Primary Care: Current Management of Common Office Problems.** UCSF. Monday-Friday.

September 24-27—**Society for Computer Medicine.** Hilton, San Diego. Wednesday-Saturday. Contact: SCM, 1901 N. Ft. Myer Dr., Ste. 602, Arlington, VA 22209.

September 24-28—**Human Dimensions in Medicine.** UCSD at Vacation Village, San Diego. Wednesday-Sunday.

September 25—**Venereal Disease.** Calif. Venereal Disease Controllers' Assn. and CMA at Tiburon Lodge, Tiburon. Thursday. Contact: Manuel De Pinna, CMA.

September 29-October 1—**Alcoholism and Chemical Dependency Treatment—Where Do We Go From Here?** Scripps Memorial Hosp. at Vacation Village, San Diego. Monday-Wednesday. 15 hrs. $175. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110.

October 11—**Ophthalmology for the Family Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

October 13-16—**Fifth Annual Family Practice Update.** LLU. Monday-Thursday. 31 hrs. $200.

October 13-17—**Hawaii Medical Association—124th Annual Meeting.** Pacific Beach Hotel, Waikiki. Monday-Friday. Contact: HMA, 320 Ward Ave., Ste. 200, Honolulu 96814. (808) 536-7702.

October 15-18—**24th Annual Western Occupational Health Conference.** Western Occupational Med. Assn. at Hotel del Coronado, Coronado. Wednesday-Saturday. Contact: Joe Donovan, WOHC, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 16-18—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 17-19—**Nutrition for the Practicing Physician.** UCSF. Friday-Sunday.

October 24-25—**Geriatric Medicine Today.** Western Div., Am. Geriatrics Soc., at Hyatt Regency, San Francisco. Friday-Saturday. Contact: AGS, Western Div., 13220 105th Ave., Bldg. B, Rm. 61, Sun City, AZ 85351.

October 25-26—**Eight Common Problems.** UCLA. Saturday-Sunday.

October 28-31—**American Academy of Occupational Medicine.** Hyatt Regency, San Francisco. Tuesday-Friday. Contact: AAOM, 150 N. Wacker Dr., Chicago 60606.

October 30-November 1—**Postgraduate Institute on Nutrition.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

November 2-5—**California Academy of Family Physicians—Annual Scientific Assembly.** Disneyland Hotel, Anaheim. Sunday-Wednesday. Contact: William W. Rogers, Exec. Sec., CAFP, 9 First St., Rm. 900, San Francisco 94105. (415) 982-6091.

November 3-7—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $275.

November 3-7—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $290.

November 13-15—**Biofeedback and Family Practice.** UCLA and Biofeedback Society at San Jose. Friday-Saturday. Contact: UCLA.

November 13-15—**Medical-Legal Aspects of Products Liability.** UCSF. Thursday-Saturday.

November 15—**Criteria for Evaluating Pseudoscience, Cults and Holistic Medicine.** San Jose State University. Saturday. 8 hrs. $40. Contact: Susan M. Grube, MPH, Cont. Ed., San Jose State Univ., Washington Sq., San Jose 95192. (408) 277-3778.

November 21-23—**Sports Medicine: The Physician and the Injured Athlete.** UCD at Marriott Inn, Berkeley. Friday-Sunday. 12 hrs.

November 21-25—**Gerontological Society—Annual Scientific Meeting.** Town and Country Hotel, San Diego. Friday-Tuesday. Contact: Dr. Eugene J. Towbin, VA Hospital, Little Rock, AR 72206.

December 5-7—**Human Sexuality.** Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

August 13—**OB-GYN Sessions—Univ. of Washington** (Anchorage). Wednesday. Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 277-6891.

MONTANA

October 2-4—**Montana Medical Association Annual Meeting.** Thursday-Saturday. Bozeman. Contact: Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

IDAHO

July 23-26—**Idaho Medical Association.** Wednesday-Saturday. Sun Valley. Contact: Idaho Medical Association, 407 West Bannock St., P.O. Box 2668, Boise, ID 83701. (208) 344-7888.

August 22—**Intermountain Infectious Disease Symposium.** Idaho Falls. Friday. Intermountain Experience Center. Contact: DeVon Hale, MD, P.O. Box 1602, Idaho Falls, ID 83401. (208) 529-0072.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue. Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

MEDICINE

September 5-6—**Current Perspectives on Rheumatology.** Ashland, Friday-Saturday. Ashland Hills Inn. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

November 14-15—**Symposium on Critical Care Medicine.** Portland, Friday-Saturday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 23-25—**Northwest Review of Obstetrics & Gynecology.** Portland, Thursday-Saturday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

PSYCHIATRY

September 13—**Movement Disorders.** Portland, Saturday. OMA Headquarters, 5210 SW Corbett Ave., Portland, OR 97201. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

September 18-19—**Dermatology for the Non-Dermatologist.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

September 26—**Shaw Memorial Lectures on Geriatric Medicine.** Portland, Friday. Oregon Medical Association Building. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

October 3-4—**Washington State Medical Association Annual Meeting Scientific Program.** Vancouver, WA/Portland, OR. Friday-Saturday. Thunderbird-Jantzen Beach. Contact: Mrs. Marcia Wahlman, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA 98121. (206) 623-4801.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

July 25-26—**Seafair II Anesthesia Meeting**—Washington State Society of Anesthesiologists. Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: Sandra McDonald, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

July 30-August 1—**Psychopharmacology for the Elderly.** Seattle. Thursday-Friday. Health Sciences Auditorium, U/W. Contact: U/W School of Medicine Div. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

August 21-22—**Current Concepts in Neonatal and Perinatal Medicine.** Seattle. Monday-Tuesday. Health Sciences Auditorium, U/W School of Medicine, Div. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

September 11-12—**Arthritis Days.** Seattle. Thursday-Friday. Hilton Hotel. Contact: Pamela Lindquist, Western Washington Chapter, Arthritis Foundation, 710 Second Ave., Seattle, WA 98104. (206) 622-2481.

September 21-23—**Emergency Medicine in Office Practice.** Walla Walla. Sunday-Tuesday. Walla Walla General Hospital. Contact: Max W. Hammonds, MD, Director, Continuing Medical Education, Walla Walla General Hospital, 1025 South Second Avenue, P.O. Box 1398, Walla Walla, WA 99362. (509) 525-0480.

September 25-28—**The Spine, Advances in Practical Management.** Seattle. Thursday-Sunday. Olympic Hotel. Contact: U/W School of Medicine, Div. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

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September 27—**Annual Cancer Symposium: Current Concepts in Gynecological Malignancies.** Tacoma. Saturday. Tacoma General Hospital. Contact: Karen Tilley, Department of Oncology, Tacoma General Hospital, 315 South K Street, Tacoma, WA 98405. (206) 597-6964.

October 3-4—**Washington State Medical Association Annual Meeting Scientific Program.** Vancouver, WA/Portland, OR. Friday-Saturday. Thunderbird-Jantzen Beach. Contact: Mrs. Marcia Wahlman, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA 98121. (206) 623-4801.

November 6-9—**United States Section, International College of Surgeons Annual Meeting.** Las Vegas, NV. Thursday-Sunday. Aladdin Hotel. Contact: Franklin R. Smith, MD, 942 Medical & Dental Bldg., Seattle, WA 98101. (206) 682-1944.

November 13-15—**Street Drugs.** Seattle. Thursday-Saturday. Park Hilton Hotel. Contact: Marilyn Carlson, Northwest Hospital Education & Training Dept., 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ex. 686.

November 13-15—**Topics in Emergency Medicine.** Seattle. Thursday-Saturday. Seattle Hyatt House (Sea-Tac). Contact: Joan Palmer, c/o WSHA, 419 Occidental Avenue South, Seattle, WA 98104. (206) 624-7240.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

July 17-18
SPONSOR: University of Utah
TITLE: **Third Annual Peri-Natal Conference**
LOCATION: Park City
FEE: To be announced
CREDIT: To be announced
CONTACT: Margaret Watkins, MD (801) 363-1221

July 25-26
SPONSOR: Iron County Medical Society
TITLE: **11th Annual Iron County Medical Society Meeting**
LOCATION: Cedar City, Utah
FEE: To be announced
CREDIT: To be announced
CONTACT: J. Garth Chatterley, MD (801) 586-9447

August 1-9
SPONSOR: University of Utah
TITLE: **2nd Annual Postgraduate Radiology Conference**
LOCATION: Veendam Cruise—Vancouver to Alaska
FEE: $300.00
CREDIT: 33 hours
CONTACT: David G. Bragg, MD (801) 581-8188

August 7-8
SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

August 8-9
SPONSOR: Utah Ophthalmological Society
TITLE: **Annual Shakespeare Festival Meeting**
Speaker: Frederick H. Reeser, MD, Medical College of Wisconsin, Milwaukee
LOCATION: Town & Country Inn, Cedar City, Utah
FEE: Members $40.00
Non-members $75.00
CREDIT: 6 hours
CONTACT: A. Thomas Williams, MD (801) 268-6111

August 15
SPONSOR: University of Utah
TITLE: **Antimicrobial Agents in Serious Infections in the Immunocompromised Host**
LOCATION: Classroom A, University Medical Center
FEE: None
CREDIT: 7 hours
CONTACT: Charles Smith, MD (801) 581-8811

August 26-28
SPONSOR: VA Regional Medical Education Center
TITLE: **Conflict, Confrontation, and Stress**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Alan Lundgren (801) 582-1565, Ext. 1100

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Carbon Hospital, Washington Park, Price 84501. (801) 637-1123
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84107 (801) 262-3461
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UU: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

September 11
SPONSOR: Rocky Mountain Center for Occupational and Environmental Health
TITLE: **Occupational Health for the 1980's**
LOCATION: Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

September 12
SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Medical Management of Ischemic Heart Disease**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: 3 hours
CONTACT: Stan Everett (801) 350-1004

September 18-20
SPONSOR: University of Utah
TITLE: **Preceptor Teaching Skills**
LOCATION: Snowbird, Utah
FEE: $15.00
CREDIT: 10.5 hours
CONTACT: Donna Harris (801) 581-8250

September 22-25
SPONSOR: VA Regional Medical Education Center
TITLE: **Sexual Health**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: George Keiser, PhD (801) 582-1565, Ext. 1100

September 30-October 3
SPONSOR: University of Utah
TITLE: **Utah State Medical Association Scientific Meeting**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: Up to 12 hours
CONTACT: Maxcine Fry (801) 355-7477

October 1-2
SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

October 10-11
SPONSOR: University of Utah/The Upjohn Company
TITLE: **2nd Fall Arthritis Conference—Rheumatology: Clinical Assessment for the Practicing Physician**
LOCATION: Park City, Utah
FEE: $70.00
CREDIT: 11 hours
CONTACT: Mark Mueller, MD (801) 581-7724

October 16
SPONSOR: LDS Hospital (with Intermountain Thoracic Society, Utah Heart Association and University of Utah)
TITLE: **Postgraduate Course—Pulmonary Heart Disease**
LOCATION: LDSH
FEE: To be announced
CREDIT: 6 hours
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

November 6
SPONSOR: LDS Hospital
TITLE: **Pulmonary Heart Disease**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

December 12
SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Hypertension**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

January 24-31
SPONSOR: University of Utah
TITLE: **6th Annual Snowbird Radiology Conference**
LOCATION: Snowbird
FEE: To be announced
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8188

February 9-12
SPONSOR: University of Utah
TITLE: **10th Annual Family Practice Refresher Course**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 28 hours
CONTACT: David N. Sundwall, MD (801) 581-8633

February 15-20
SPONSOR: University of Utah
TITLE: **Update on Clinical Microbiology and Immunology**
LOCATION: Park City
FEE: To be announced
CREDIT: 24 hours
CONTACT: John M. Matsen, MD (801) 581-5514

February 20-24
SPONSOR: University of Utah
TITLE: **26th Annual Postgrad Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: 16 hours
CONTACT: Theodore H. Stanley, MD (801) 581-6393

February 21-24
SPONSOR: University of Utah
TITLE: **OB-GYN 22nd Annual Postgrad Course**
LOCATION: Park City
FEE: To be announced
CREDIT: 16.5 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-27
SPONSOR: University of Utah/Intermountain Pediatric Society/American Academy of Pediatrics
TITLE: **Common Problems in Pediatrics III**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 16 hours
CONTACT: Bruce Buehler, MD (801) 581-7877

February 25-28
SPONSOR: University of Utah
TITLE: **Gynecologic Oncology Course**
LOCATION: To be announced
FEE: To be announced
CREDIT: 16.5 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-March 7
SPONSOR: University of Utah
TITLE: **Midwinter Radiology Pacific Cruise Meeting**
LOCATION: Departs from Los Angeles
FEE: $300.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

February 28-March 7
SPONSOR: University of Utah
TITLE: **6th Annual Advances in Internal Medicine**
LOCATION: Snowbird
FEE: $225.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1981—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 22-26, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 24-27, 1980, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 13-17, 1980, Pacific Beach Hotel, Waikiki.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1980, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Convention: November 7-8, 1980, Kachina Lodge, Taos.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 30-October 3, 1980, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA/Portland, OR.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 23-27, 1980, Snow King Inn, Jackson.

February 28-March 7

SPONSOR: University of Utah
TITLE: **Nutrition and Contemporary Medicine**
LOCATION: Park City
FEE: $200.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 7-14

SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 14-21

SPONSOR: University of Utah
TITLE: **3rd Annual Park City Radiology Conference: Neuroradiology**
LOCATION: Park City
FEE: $240.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

April 8-10

SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ University of Arizona Center for Occupational Safety and Health/University of Texas Health Science Center, School of Public Health
TITLE: **3rd Annual Park City Environmental Health Conference: Legal and Ethical Dilemmas in Occupational Health**
LOCATION: Prospector Square Lodge, Park City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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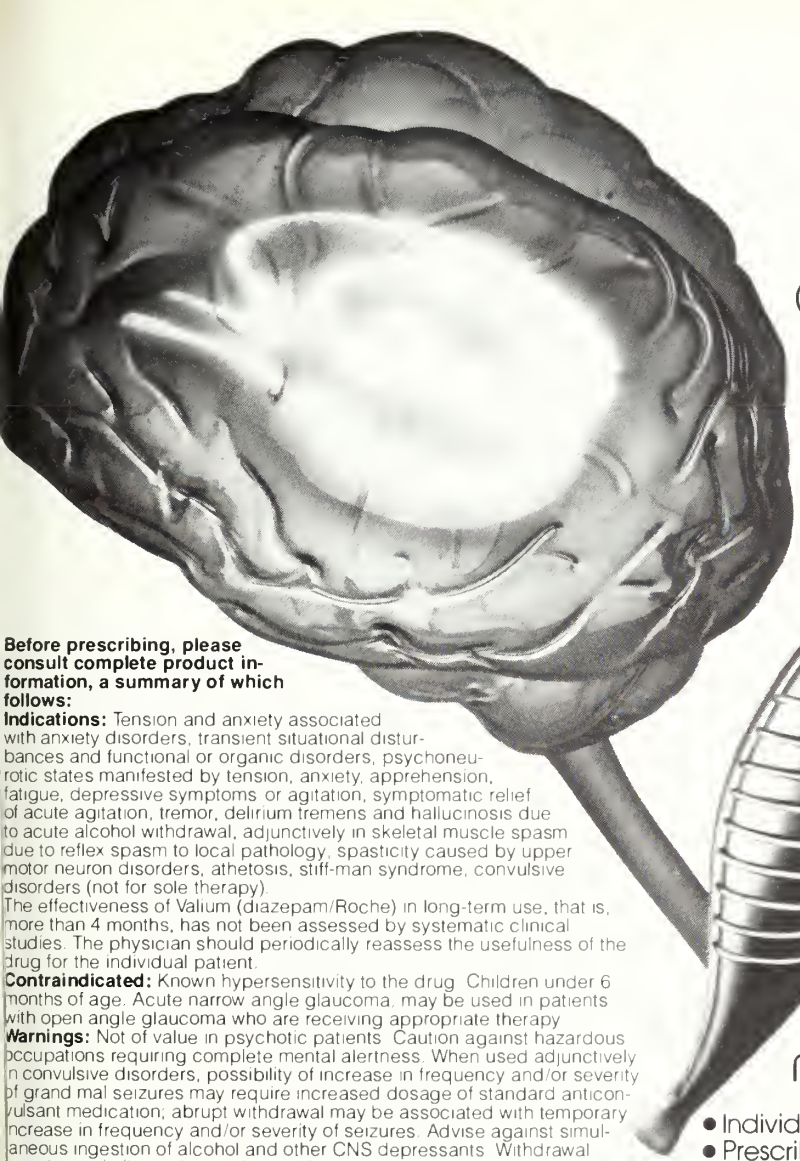

Only Valium® (diazepam/Roche) is indicated in anxiety and tension states and as an adjunct in the relief of skeletal muscle spasm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety associated with anxiety disorders, transient situational disturbances and functional or organic disorders, psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation, symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).
The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported. Should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available in trays of 10.

General guidelines for the prescribing and appropriate use of minor tranquilizers

- Individualize dosage for maximal beneficial effect.
- Prescribe the specific quantity needed until the next checkup period, schedule frequent, periodic reexaminations to monitor results of therapy.
- Establish treatment goals and gradually discontinue medication when these have been met.
- Avoid prescribing for individuals who appear dependency-prone or whose histories indicate the potential for misuse of psychoactive substances, including alcohol.
- Caution patients against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving.
- Advise patients against the ingestion of alcoholic beverages while undergoing therapy with minor tranquilizers.
- Counsel patients to follow label directions, keep medication out of children's reach, and dispose of unused or old medication.
- Caution patients against giving medication to others.
- Avoid abrupt cessation of extended therapy by tapering dosage before discontinuing medication.

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Indicated in anxiety and tension states and as an adjunct in the relief of skeletal muscle spasm

Please see summary of product information on preceding page.

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CONSIDER THE COMPARATIVE EFFICACY OF DALMANE® VS.
(flurazepam HCl/Roche)
OTHER SLEEP MEDICATIONS

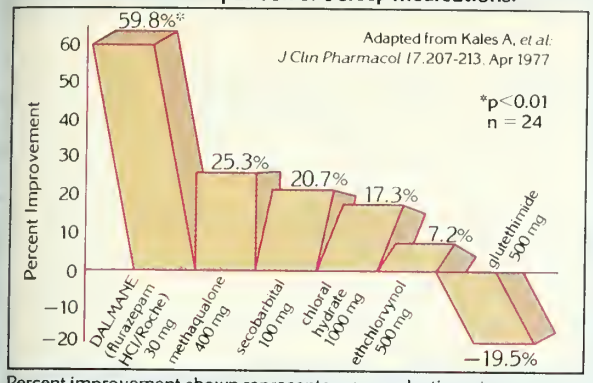
Sleep research laboratory studies show Dalmane (flurazepam HCl/Roche) **more effective for more nights than other sleep medications tested**

Polygraphic appraisal of sleep in 36 insomniac subjects over 14 consecutive nights, proved that of the 9 medications* tested, only Dalmane remained significantly effective for the duration of the study.[1]

While it is reassuring that efficacy can be maintained for this period of time if needed, pharmacological treatment of insomnia should be initiated with the lowest possible effective dose and continued only as long as judged appropriate to achieve a therapeutic goal.

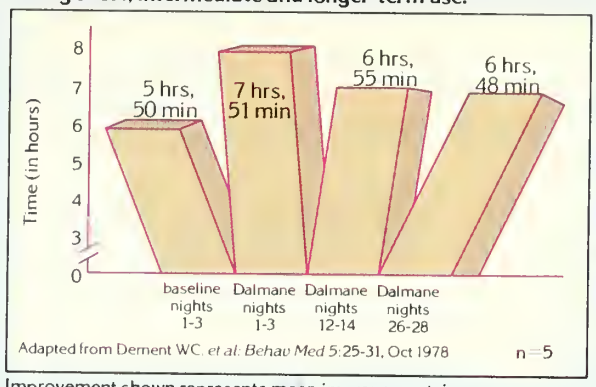
*The drugs studied included 7 commercially available and 2 investigational hypnotics.

Percent decrease in total wake time after 12-24 nights of administration: a comparison of 6 sleep medications.



Percent improvement shown represents mean reductions, in minutes, of insomnia in the parameter of total wake time.

Dalmane (flurazepam HCl/Roche) improved sleep during short, intermediate and longer-term use.



Improvement shown represents mean improvement, in hours, of total sleep time.

Additional studies showed that Dalmane (flurazepam HCl/Roche) continued to provide effective insomnia relief for 28 consecutive nights of use

Two sleep research laboratory studies with a total of 10 insomniacs investigated for 280 subject nights, conducted at geographically separated university medical centers, proved the longer-term usefulness of Dalmane.[2,3]

Although insomnia is often transient, it may sometimes be necessary to continue treatment for periods up to 4 weeks. If so, careful assessment of the patient's medical profile should be made, with special attention to periodic blood counts and liver and kidney function tests.

Plus, efficacy proved in elderly insomniacs with the 15 mg dosage *h.s.*

Six insomniac patients, aged 67 to 82 years, averaged 1 hour and 23 minutes more sleep nightly during treatment with Dalmane for a period of one week.[4] It should be kept in mind that sleep medication may not always be appropriate for elderly individuals who complain of insomnia. Contributing factors may include requirements for less sleep than in younger years or the establishment of poor sleeping habits, such as napping during the day.

REFERENCES:

1. Kales A, *et al: J Clin Pharmacol 17*:207-213, Apr 1977
2. Dement WC, *et al: Behav Med 5*:25-31, Oct 1978
3. Kales A, *et al: Clin Pharmacol Ther 19*:576-583, May 1976
4. Frost JD Jr, De Lucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979

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flurazepam HCl/Roche

15-mg and 30-mg capsules

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Please turn page for a summary of product information.

PROTOCOL FOR INSOMNIA MANAGEMENT

- ☐ Treat physical and/or psychological factors that may underlie an inability to sleep.
- ☐ Thoroughly question and evaluate new patients who specifically request sleep medications.
- ☐ Consider other medications the patient may be taking (including alcoholic beverages) and be aware of possible drug interactions.
- ☐ Select a sleep medication with objectively documented proof of efficacy and a wide margin of safety.
- ☐ Initiate treatment at the lowest effective dose for the period of time deemed necessary to achieve a reasonable therapeutic goal.
- ☐ Monitor response to therapy and, based upon patient reassessment, determine need for continuing medication on an individual basis.
- ☐ Advise patients who ingest alcoholic beverages or other CNS depressants against doing so while on sleep medication. CNS stimulants such as caffeine should also be discontinued.
- ☐ Caution patients against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle shortly after ingesting the drug. In addition, as with all CNS depressants, patients may have reduced motor performance while on hypnotic therapy and should be advised accordingly.
- ☐ Avoid prescribing for suicidal or dependency-prone individuals whose histories indicate an inability to handle any psychoactive substances including alcohol.

DALMANE® ⓒIV

flurazepam HCl/Roche

One 15-mg capsule *h.s.*—recommended initial dosage for elderly or debilitated patients.
One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, e.g., excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg recommended initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

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Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

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cefaclor

Pulvules®, 250 and 500 mg

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below.

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory tests results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

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* Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note: Ceclor® (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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7. Data on file, Eli Lilly and Company.
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979.

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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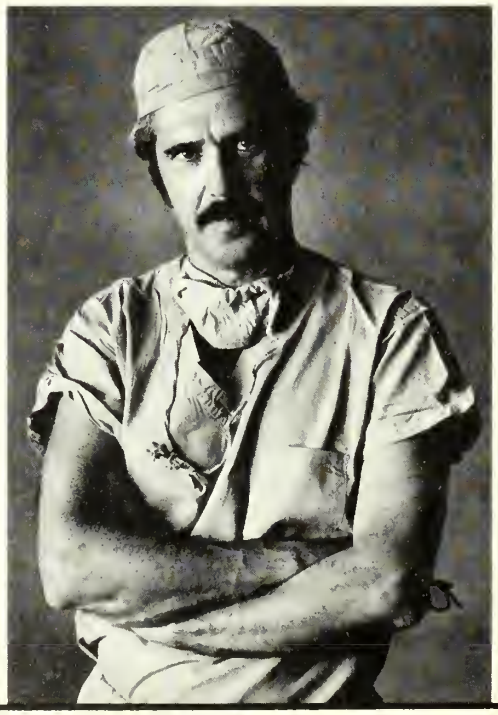

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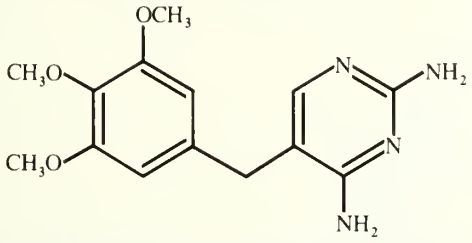

CLINICAL PHARMACOLOGY: Trimethoprim is rapidly absorbed following oral administration. Mean peak serum levels of approximately 1.0 mcg/ml occur 1 to 4 hours after oral administration of a single 100 mg dose. The half-life of trimethoprim is 8 to 10 hours. Trimethoprim exists in the blood as free, protein-bound and metabolized forms. Approximately 44% of trimethoprim is protein-bound in the blood. The free form is considered to be the therapeutically active form.

Excretion of trimethoprim is chiefly by the kidneys through glomerular filtration and tubular secretion. Urine concentrations of trimethoprim are considerably higher than are the concentrations in the blood. Trimethoprim urine levels, after a single oral dose of 100 mg, ranged from 30 to 160 mcg/ml during the 0 to 4 hour period and declined to approximately 18 to 91 mcg/ml during the 8 to 24 hour period.

After oral administration, 50% to 60% of trimethoprim is excreted in the urine within 24 hours, approximately 80% of this being unmetabolized trimethoprim.

Microbiology: Trimpex blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. Thus, Trimpex selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of Trimpex includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*.

Representative Minimum Inhibitory Concentrations
For Trimethoprim-Susceptible Organisms

Bacteria	Trimethoprim MIC—mcg/ml (Range)
Escherichia coli	0.05—1.5
Proteus mirabilis	0.5—1.5
Klebsiella pneumoniae	0.5—5.0
Enterobacter species	0.5—5.0

The recommended quantitative disc susceptibility method[1,2] may be used for estimating the susceptibility of bacteria to Trimpex (trimethoprim/Roche). Reports from the laboratory giving results of the standardized test using the 5 mcg trimethoprim disc should be interpreted according to the following criteria:

Organisms producing zones of 16 mm or greater are classified as susceptible whereas those producing zones of 11 to 15 mm are classified as having intermediate susceptibility. A report from the laboratory of "Susceptible to trimethoprim" or "Intermediate susceptibility to trimethoprim" indicates that the infection is likely to respond when, as in uncomplicated urinary tract infections, effective therapy is dependent upon the urine concentration of trimethoprim.

Organisms producing zones of 10 mm or less are reported as resistant, indicating that other therapy should be selected.

Dilution methods for determining susceptibility are also used, and results are reported as the minimum drug concentration inhibiting microbial growth (MIC).[3]

If the MIC is 8 mcg per ml or less, the microorganism is considered "susceptible." If the MIC is 16 mcg per ml or greater, the microorganism is considered "resistant."

Normal vaginal and fecal flora are the source of most pathogens causing urinary tract infections. It is therefore relevant to consider the suppressive effect of trimethoprim in these sites.

Concentrations of trimethoprim in vaginal secretions are consistently greater than those found simultaneously in the serum, being typically 1.6 times the concentration of simultaneously obtained serum samples. Sufficient trimethoprim is excreted in the feces to markedly reduce or eliminate trimethoprim-susceptible organisms from the fecal flora.

The dominant fecal organisms (non-*Enterobacteriaceae*), *Bacteroides* spp. and *Lactobacillus* spp., are not susceptible to trimethoprim levels obtained with the recommended dosage.

INDICATIONS AND USAGE: For the treatment of initial episodes of uncomplicated urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae* and *Enterobacter* species.

Cultures and susceptibility tests should be performed to determine the susceptibility of the bacteria to trimethoprim. Therapy may be initiated prior to obtaining the results of these tests.

CONTRAINDICATIONS: Trimpex (trimethoprim/Roche) is contraindicated in individuals hypersensitive to trimethoprim and in those with documented megaloblastic anemia due to folate deficiency.

WARNINGS: Experience with trimethoprim alone is limited, but it has been reported rarely to interfere with hematopoiesis, especially when administered in large doses and/or for prolonged periods.

The presence of clinical signs such as sore throat, fever, pallor or purpura may be early indications of serious blood disorders. Complete blood count should be obtained if any of these signs are noted in a patient receiving trimethoprim and the drug discontinued if a significant reduction in the count of any formed blood element is found.

PRECAUTIONS: *General:* Trimethoprim should be given with caution to patients with possible folate deficiency. Folates may be administered concomitantly without interfering with the antibacterial action of trimethoprim. Trimethoprim should also be given with caution to patients with impaired renal or hepatic function.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Trimethoprim has been shown to be teratogenic in the rat when given in doses 40 times the human dose. In some rabbit studies, the overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses 6 times the human therapeutic dose. While there are no large well-controlled studies on the use of trimethoprim in pregnant women, Brumfitt and Pursell[4] reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim plus sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received trimethoprim plus sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim may interfere with folic acid metabolism, Trimpex should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Trimethoprim is excreted in human milk. Because trimethoprim may interfere with folic acid metabolism, caution should be exercised when Trimpex is administered to a nursing woman.

Pediatric Use: Safety of trimethoprim in infants under two months of age has not been demonstrated. The effectiveness of trimethoprim has not been established in children under 12 years of age.

ADVERSE REACTIONS: The adverse effects encountered most often with trimethoprim were rash and pruritus. Other adverse effects reported involved the gastrointestinal and hematopoietic systems.

Dermatologic Reactions: Rash, pruritus and exfoliative dermatitis. At the recommended dose of 100 mg b.i.d., the incidence of rash is 2.9%. In clinical studies which employed high doses of Trimpex, an elevated incidence of rash was noted. These rashes were maculopapular, morbilliform, pruritic and generally mild to moderate, appearing 7 to 14 days after the initiation of therapy.

Gastrointestinal Reactions: Epigastric distress, nausea, vomiting and glossitis.

Hematologic Reactions: Thrombocytopenia, leukopenia, neutropenia, megaloblastic anemia and methemoglobinemia.

Miscellaneous Reactions: Fever, elevation of serum transaminase and bilirubin, and increases in BUN and serum creatinine levels.

OVERDOSAGE: *Acute:* Signs of acute overdosage with trimethoprim may appear following ingestion of 1 gram or more of the drug and include nausea, vomiting, dizziness, headaches, mental depression, confusion and bone marrow depression (see CHRONIC OVERDOSAGE). Treatment consists of gastric lavage and general supportive measures. Acidification of the urine will increase renal elimination of trimethoprim. Peritoneal dialysis is not effective and hemodialysis only moderately effective in eliminating the drug.

Chronic: Use of trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. If signs of bone marrow depression occur, trimethoprim should be discontinued and the patient should be given leucovorin, 3 to 6 mg intramuscularly daily for three days, or as required to restore normal hematopoiesis.

DOSAGE AND ADMINISTRATION: The usual oral adult dosage is 100 mg of Trimpex (trimethoprim/Roche) every 12 hours for 10 days.

The use of trimethoprim in patients with a creatinine clearance of less than 15 ml/min is not recommended. For patients with a creatinine clearance of 15 to 30 ml/min, the dose should be 50 mg every 12 hours.

The effectiveness of trimethoprim has not been established in children under 12 years of age.

HOW SUPPLIED: Tablets, containing 100 mg trimethoprim—bottles of 100; Tel-E-Dose® packages of 100; and Prescription Paks of 20.

REFERENCES:

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4. Brumfitt W, Pursell R. Trimethoprim/sulfamethoxazole in the treatment of bacteriuria in women, *J Infect Dis 128* (Suppl): S657-S663, 1973.

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THE WESTERN
Journal of Medicine

Refer to: Burt TB, MacCarter DK, Gelman MI, et al: Clinical manifestations of synovial cysts. West J Med 133:99-104, Aug 1980

Clinical Manifestations of Synovial Cysts

TODD B. BURT, MD; DARYL K. MacCARTER, MD; MARTIN I. GELMAN, MD, *and* CECIL O. SAMUELSON, MD, *Salt Lake City*

Although synovial cysts are most commonly associated with rheumatoid arthritis and osteoarthritis, they may occur in many other conditions. The clinical manifestations of these cysts are numerous and may result from pressure, dissection or acute rupture. Vascular phenomena occur when popliteal cysts compress vessels, and result in venous stasis with subsequent lower extremity edema or thrombophlebitis. Rarely, popliteal cysts may cause arterial compromise with intermittent claudication. Neurological sequelae include pain, paresthesia, sensory loss, and muscle weakness or atrophy. When synovial cysts occur as mass lesions they may mimic popliteal aneurysms or hematomas, adenopathy, tumors or even inguinal hernias. Cutaneous joint fistulas, septic arthritis or osteomyelitis, and spinal cord and bladder compression are examples of other infrequent complications. Awareness of the heterogeneous manifestations of synovial cysts may enable clinicians to avoid unnecessary diagnostic studies and delay in appropriate management. Arthrography remains the definitive diagnostic procedure of choice, although ultrasound testing may be useful.

SYNOVIAL CYSTS are fluid-filled spaces lined by synovial membrane and arise from diarthrodial joints, bursae and tendon sheaths. The first published report of a synovial cyst was made by Adams, an Irish surgeon, in 1840.[1] He described a cyst that extended from the knee joint into the popliteal space. An English surgeon, William Baker, reported his observations on synovial cysts in 1877, resulting in the common eponym Baker cysts, for popliteal cysts.[2] Subsequently, synovial cysts have been described in numerous locations although the knees, shoulders and wrists remain the most frequently involved areas.

The common manifestations of synovial cysts, particularly those associated with rheumatoid arthritis, are well known. However, vascular and neurological sequelae as well as unusual causes and sites of involvement, have received less emphasis. Our recent experience involving patients with synovial cysts has suggested greater variety in presentation than is generally appreciated. This has led to our report of three cases and a review

From the Department of Radiology, University of Utah Medical Center, Salt Lake City (Drs. Burt and Gelman), and the Arthritis Division, Department of Internal Medicine (Drs. MacCarter and Samuelson). Dr. MacCarter is now affiliated with the Rackham Arthritis Research Unit, University of Michigan, University Hospital, Ann Arbor.

Submitted, revised, December 26, 1979

Reprint requests to: Martin I. Gelman, MD, Department of Radiology, University of Utah Medical Center, Salt Lake City, UT 84132.

of the common as well as the unusual features. Awareness by physicians of the various manifestations of synovial cysts is essential for accurate, expeditious diagnosis and proper management.

Reports of Cases

CASE 1. A 34-year-old woman with long-standing seropositive rheumatoid arthritis had asymptomatic swelling at the left elbow. An examination of the joint showed a large medial swelling in the region of the antecubital fossa that was not tender to palpation. Passive and active range of motion of the elbow was limited from 15 to 90 degrees. An arthrogram showed a large synovial cyst which communicated with the elbow joint (Figure 1). The cyst was treated with joint aspiration and intra-articular corticosteroid injection, resulting in a pronounced decrease in the swelling and disappearance of the apparent flexion contracture.

This case illustrates the occurrence of a large synovial cyst in an unusual location, which may impede the full movement of a joint and simulate a flexion deformity.

CASE 2. A 64-year-old man with seropositive rheumatoid arthritis of 20 years duration had severe pain and paresthesia of the right arm. An examination of the area showed considerable swelling of the right shoulder with cystic distention anteriorly and laterally. Mild erythema and warmth suggested possible joint infection. By aspirating the glenohumeral joint we collected 45 ml of cloudy, yellowish fluid. Gram stain and cultures of the fluid were negative. An arthrogram of the shoulder showed a cyst communicating with the glenohumeral and acromioclavicular joints (Figure 2). Aspiration of the joint and subsequent cyst resection with synovectomy provided only temporary relief of symptoms, with eventual recurrence of the cyst.

This case presents an instance of a synovial cyst of the subacromial bursa that developed following a rotator cuff tear secondary to the rheumatoid process.

CASE 3. A 74-year-old woman with seropositive rheumatoid arthritis of five years duration had severe pain in the left wrist associated with numbness and paresthesia of the thumb, index and middle fingers. The pain radiated to the left elbow and was unresponsive to orally given analgesics. An examination of the joint showed considerable tenderness of the left wrist, with swelling predominantly of the volar aspect. Tinel and Phalen maneuvers were positive and a diagnosis of carpal tunnel syndrome was made. An arthrogram showed severe rheumatoid changes with narrowing of the intercarpal joint space and cartilage destruction. No communication with the area of the cystic swelling was detected. The cyst was then punctured and injected with contrast media. No movement of the fluid from the cyst to the wrist

Figure 1.—Arthrogram showing a synovial cyst of the elbow communicating with the elbow joint.

Figure 2.—Arthrogram showing a synovial cyst of the shoulder communicating with the glenohumeral and acromioclavicular joints. There is filling of the subacromial bursa (arrows), indicating an associated rotator cuff tear.

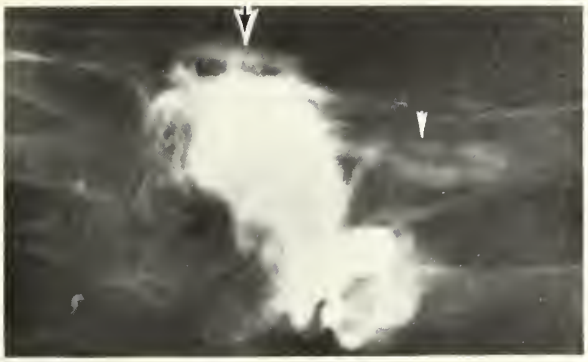

Figure 3.—Initially, arthrogram of the wrist showed no communication with cyst (dense contrast media overlying carpal bones). Cyst (larger arrow) then injected separately shows communication with flexor tendon sheath (small arrow).

joint was noted; movement of the fluid was continuous with the flexor tendon sheath (Figure 3). Treatment consisted of cyst aspiration, transverse carpal ligament resection and synovectomy. Carpal tunnel symptoms resolved postoperatively, but recurrence of the cyst was noted within five months.

This case illustrates median nerve entrapment caused by a synovial cyst of a volar flexor tendon sheath.

Discussion

Numerous pathological conditions may cause inflammation of the synovial membrane which, in turn, leads to increased production of synovial fluid in different parts of the musculoskeletal system, and may result in the formation of synovial cysts. A plethora of terms and eponyms have been coined to describe both synovial and nonsynovial cysts. Unfortunately, because of a general lack of familiarity with these terms, this has led to more confusion than clarity. A brief review of terminology is therefore warranted.

Synovial fluid, which can be considered a form of liquid ground substance, is also known as synovia.[3] The term synovia (Latin: syn-, with + ovum, egg) is first found in the writings of Paracelsus (1493-1541). He credited the origin of the word to early wound surgeons who compared the consistency of the gelatinous joint fluid with that of egg white.[4] Synovia has a complex structure composed mostly of mucopolysaccharides (hyaluronic acids), proteins and occasional cells consisting of monocytes, lymphocytes and macrophages.[3(pp13-14)] Synovial fluid is produced and absorbed by the synovial membrane, which is derived from embryonic mesenchyme, and lines the nonarticulating parts of diarthrodial joints, synovial bursae and synovial tendon sheaths.[5] This unique structure allows for movement between contiguous tissues with a remarkable lack of friction and for nutrition of the avascular articular cartilage of joints.

In pathological conditions, fluid can distend a bursa or tendon sheath, resulting in formation of a cyst. A synovial joint cyst results from herniation of the synovial membrane through the joint capsule or enlargement of a bursa communicating with the joint. Other cysts that lack a true synovial membrane and are lined by reactive fibrous tissue or by preexisting anatomical structures (such as tendons, muscles and bone), should be referred to as pseudocysts. Geodes are juxta-articular bone cysts that lack a true epithelial lining and are a form of pseudocyst.[6] A ganglion is a cystic swelling adjacent to a tendon sheath or joint capsule which contains mucoid fluid, but which is only infrequently lined by a synovial membrane.[7] Therefore, most ganglia are pseudocysts.

Etiology

Any inflammatory, degenerative or traumatic condition that produces an effusion may contribute to the development of a synovial joint cyst. These cysts are most commonly associated with osteoarthritis or rheumatoid arthritis. In one study involving patients who had had rheumatoid arthritis affecting the knees for more than five years, the frequency of popliteal cysts approached 30 percent.[8] In adults, synovial joint cysts have also been described in association with tuberculosis, osteochondromatosis, gout, pseudogout, giant cell tumor, brucellosis, Sjögren* syndrome, Reiter disease, systemic lupus erythematosus, psoriatic arthritis, pigmented villonodular synovitis, meniscal tears, neuropathic arthritis and juvenile rheumatoid arthritis.[6,9-12] In children popliteal cysts occur primarily as the result of trauma.[12]

Synovial bursa and tendon sheath distention, with subsequent cyst formation, are associated with trauma or excessive exercise, rheumatoid arthritis, gout or pyogenic infections, although the cause in many instances is unknown. Bursitis and tenosynovitis with cyst formation may also

*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

occur with other infectious, systemic and rheumatic diseases.[3(p88)]

Location

Synovial joint cysts occur most frequently in the popliteal space and are called Baker cysts. However, they are often observed in the shoulders, wrists, fingers and feet as well.[6] Uncommon locations include the elbows, ankles, hips and apophyseal joints of the spine.[13,14]

Cysts of the tendon sheaths are often seen in the wrists and fingers. Distended and painful bursae over the ischial tuberosity (weaver's bottom), olecranon (miners' elbow), or prepatellar region (housemaid's knee) are not unusual.[6,15]

Pathophysiology

A true synovial joint cyst results from herniation of the synovial membrane through the joint capsule or from enlargement of a bursa already communicating with the joint. In one series describing popliteal cysts, 56 percent were of bursal origin (semimembranosus and gastrocnemius), 31 percent from herniation and 13 percent were of indeterminate origin.[9] Formation of synovial joint cysts by herniation occurs when a pathological process produces an effusion of fluid at the joint, with subsequent increase in intra-articular pressure. This increased pressure leads to extrusion of the synovial membrane through a segment of the joint capsule (often weakened by the same pathological process), with resultant cyst formation. Genovese[8] has suggested that this represents a protective mechanism for decompression of a diseased joint.

A valvular mechanism allowing only unidirectional flow of synovial fluid from the joint into the cyst has been suggested by Jayson and Dixon.[16] They summarized two possibilities which could result in this sort of valve: a ball-valve mechanism resulting from inspissated fibrin and cell debris within the cyst or a Bunsen valve resulting from the enlarging cyst compressing its own channel of communication.

Vascular Manifestations

Synovial cysts that cause vascular complications are observed most frequently in the popliteal region where they may cause popliteal vessel compression. Direct pressure on venous and lymphatic channels can result in stasis with edema of the leg. Swett[17] reported that in several patients with edema of the leg, venography clearly illustrated both stretching and compression of popliteal veins by Baker cysts. This circumstance might also be expected to increase the risk of deep venous thrombosis as a result of stasis.

Pseudothrombophlebitis is now a well-recognized entity caused by dissection or rupture of popliteal cysts, with subsequent clinical findings mimicking deep venous thrombosis.[18] Generally, these patients have sudden pain and swelling of the calf, and may notice rapid reduction in the size of the cyst. On physical examination, warmth, erythema, swelling and even a positive Homan sign are frequently noted.[18] On occasion these patients are treated with heparin because of a misdiagnosis of acute deep venous thrombosis. Unfortunately, these patients may be placed in needless jeopardy with the correct diagnosis remaining unrecognized while inappropriate anticoagulant therapy is initiated.

Rarely, acute rupture of a popliteal cyst and deep venous thrombosis may occur simultaneously.[19] Although this is unusual, it emphasizes that both arthrography and venography should be carried out in cases in which coexistence of both processes is suspected or in which history and physical examination are consistent with either process.

Finally, synovial cysts may masquerade as aneurysms or hematomas. This may occur when a cyst lies adjacent to an artery, particularly in the femoral and popliteal regions. Arterial pulsations may be transmitted through the cyst, which may cause it to be confused with an aneurysm. Generally, a careful physical examination will easily differentiate a cyst from a vascular lesion, although arthrography or ultrasound testing may be necessary in some cases.

Neurological Manifestations

Neurological manifestations may result from nerve compression by synovial cysts. These may occur at any point where a peripheral nerve is trapped between an enlarging cyst and an inelastic structure (such as bone or fibrous structures). Entrapment neuropathies are common complications in patients with long-standing rheumatoid arthritis, and are characterized by pain, paresthesia, sensory loss, weakness or muscle wasting. Nakano[20] has estimated that approximately 45 percent of patients with chronic rheumatoid arthritis, severe peripheral joint involvement or subcutaneous nodules have one or more entrapment neuropathies during the course of their ill-

ness. Nerve compression by synovial cysts, however, is only one of several possible causes of entrapment in rheumatoid patients. Other mechanisms of compression may include tissue inflammation with edema and direct pressure secondary to bony malalignment from destruction of the rheumatoid joint. In addition, clinicians must be fully aware that noncompressive neuropathies secondary to vasculitis, nutritional deficiency and demyelination may be encountered in rheumatoid patients.

The carpal tunnel syndrome as discussed in case 3 is the most frequently encountered entrapment neuropathy of rheumatoid arthritis. Because the transverse carpal ligament is a relatively inflexible structure, volar tenosynovitis in this area often produces pressure on the median nerve. In approximately 25 percent of patients with rheumatoid arthritis the carpal tunnel syndrome develops; however, the proportion of cases resulting from entrapment by a synovial cyst is not known.[21]

Common peroneal nerve compression by a popliteal cyst may result in paresis of the peroneal and tibialis anterior muscles and extensor muscles of the digits. Sensory loss may also be present on the side of the leg and dorsum of the foot. Infrequently, rheumatoid synovial cysts result in entrapment or compression of the ulnar, radial or posterior tibial nerves.[20]

An unusual neurological complication consisting of extradural compression of the spinal cord by a synovial cyst arising from a lumbar apophyseal joint was described by Linquist.[14] Cord compression resulted in radicular pain involving the anterior thigh and buttocks. Following laminectomy and cyst resection the patient recovered uneventfully. Interestingly, no reports of neurological sequelae from nonrheumatoid synovial cysts were found in the literature, although the potential for nerve compression is still present in such cases.

Miscellaneous Manifestations

In patients with rheumatoid arthritis, synovial cysts may occasionally erode through adjacent tissues and rupture through the skin, forming a cutaneous joint fistula. This type of fistula may arise either spontaneously or secondarily to a septic joint. Shapiro[22] reported cutaneous joint fistulas involving the metatarsal-phalangeal, hip and knee joints in rheumatoid patients. Although on physical examination several of these mimicked a septic process, Gram stain and culture of the synovial fluid were negative. These fistulas arise spontaneously and are therefore assumed to result from the rheumatoid inflammatory process. Cutaneous joint fistulas have also been reported arising spontaneously from noninfected popliteal cysts following a knee operation.[23] Septic arthritis, however, is a well-recognized complication in patients with rheumatoid arthritis and may occasionally result in formation of a fistula. In these patients cultures of the sinus and synovial fluids grow the same organism.

A synovial cyst may also appear as a mass adjacent to a joint and mimic a tumor, adenopathy or hematoma. Samuelson and Ward[13] reported a rheumatoid synovial cyst of the hip presenting as an apparent inguinal hernia. Compression of the bladder by a hip synovial cyst with symptoms of dysuria, frequency, nocturia and dribbling was described by Watson.[24] Large cysts arising in the shoulder may mimic adenopathy or tumor by dissection into the axilla. Swelling of synovial cysts may also limit the full range of motion of a joint as occurred in patient 1. Rupture of the rotator cuff of the shoulder may precede or be associated with the formation of a subacromial synovial cyst as illustrated in the case of patient 2.

Radiology

The radiographic diagnosis of synovial cysts has been reviewed by various authors.[25,26] Ultrasound testing, radionuclide scanning and computerized tomography (CT) have not been shown to provide definite advantages over arthrography. Radioactive isotope scans have been shown to be accurate in diagnosing popliteal cyst rupture; however, joint puncture and infusion of the isotope are still required. Also, these scans are of little help in showing other joint abnormalities such as meniscal tears, that may lead to synovial cysts. Ultrasound testing is an excellent method for detecting synovial cysts, but frequently is incapable of showing cysts that have already ruptured.[27] Cooper[28] recently reported a limited study which showed that computerized tomography could not delineate popliteal cysts that had not already been injected with contrast media. Furthermore, the appearance of the cyst on a CT scan after injection of air or contrast media adds little to the information obtained by conventional arthrography. At present, arthrography remains the definitive procedure for evaluation of synovial cysts, except when puncture of the cyst or joint is contraindicated or technically difficult, as in

children. In these instances, ultrasound tests may have value.

Treatment

Most synovial cysts do not require specific treatment because they are asymptomatic and often resolve spontaneously or with treatment of the underlying disease process. Appropriate treatment of symptomatic synovial cysts generally includes rest, heat and aspiration of the fluid in the joint. Direct aspiration or injection of a true synovial cyst of the knee or elbow is usually best avoided because damage may result to important neurovascular structures, although arthrocentesis of the adjacent joint is often helpful.

In cases of ruptured popliteal cysts, elevation of the leg may also give relief. Application of icepacks may be beneficial in cases of acute dissection of synovial cysts, regardless of the location. Intra-articular injection of steroids is often helpful and may relieve pain rapidly, but must be used cautiously. Surgical synovectomy is sometimes followed by recurrence of the cyst. However, anterior synovectomy of the knee alone, maintaining the protective function of the connecting bursa, has been shown to be successful.

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Hypoglycemia and Accidental Hypothermia in an Alcoholic Population

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Hypoglycemia is but one of a number of causes of hypothermia, but is important to keep in mind as a possible precipitating or concurrent event even in those cases in which there are other obvious explanations for decreased body temperature (exposure, alcoholism, starvation, sepsis or hypothyroidism). Hypoglycemia may occur in as many as 40 percent of very cold patients, and be clinically unrecognized because symptoms are masked by the hypothermia itself. Although serum glucose levels are depressed, a cold-induced renal tubular glycosuria may occur. Glucose in the urine, therefore, cannot be used as assurance of hyperglycemia in a hypothermic patient. And, although cold protects against serious end organ damage from hypoglycemia by decreasing tissue metabolic need for glucose, a serum specimen should be drawn for glucose determination in all hypothermic patients and a 50 percent glucose solution immediately given intravenously. If this is not done, serum glucose levels may plummet as the patient is rewarmed and begins to shiver.

HYPOTHERMIA DURING INSULIN THERAPY and insulin-independent hypoglycemia has been recognized for many years.[1-4] The hypothermia of hypoglycemia is a result of intracellular glucopenia in the hypothalamus, probably mediated by an alteration of neurohumoral controls.[5] Teleologically, it seems a protective *turning down* of body temperature, and therefore of metabolic rate, in the face of inadequate fuel supply.

Hypothermia may also cause hypoglycemia. In cases of prolonged hypothermia[6] and in starved hypothermic persons,[7] low serum glucose values are usual. In addition, a cold-induced renal tubular glycosuria may actually contribute to hypoglycemia by wasting glucose through the kidneys.[7]

Other influences in cases of hypothermia oppose the development of hypoglycemia. Tissue consumption of glucose decreases as temperature falls.[8-13] Decreased pancreatic insulin release,[14-17] decreased tissue sensitivity to insulin,[10] liver dysfunction[8] and cold-induced pancreatitis[18-23] may all contribute to elevation of serum glucose in hypothermic patients.

Excess ingestion of alcohol is a common associate of accidental hypothermia[18,24-28] and alcohol may induce hypoglycemia.[29-31] The case records of 22 hypothermic, predominantly alcoholic patients were obtained from medical records by selecting the diagnostic code for hypothermia. These records were retrospectively reviewed in

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order to study the relationship of hypothermia to glucose levels.

Patients and Methods

The 22 patients (19 men and 3 women) all were admitted by way of the emergency room of the San Francisco General Hospital between 1975 and 1977. All had rectal temperatures no higher than 34.4°C (94°F). All but two were alcoholic. Only one was younger than 50 years. Of the 22 patients, 12 were found indoors, in apartments or hotel rooms.

In all 22 a serum specimen for glucose determination was drawn on entry, before parenteral administration of glucose. The highest serum glucose value was 314 mg per dl in a patient with chronic pancreatitis (case 2). The lowest was 13 mg per dl in an alcoholic patient (case 11). In nine patients (41 percent) serum glucose levels were lower than 50 mg and in five (23 percent) they were higher than 150 mg per dl. Analysis of urine specimens showed three patients to be glycosuric. Of these, two had concurrent serum glucose levels of less than 80 mg per dl. In one patient the urine reaction for glucose was 2+, with a serum glucose value of 18 mg per dl. In the other the urine reaction for glucose was 1+, with a serum glucose level of 76 mg per dl (cases 15 and 6).

Notes in the case records referring to nutritional status were made in only two cases: One man was "debilitated," another "thin." In six patients, however, there were serum albumin values of less than 2.5 grams per dl; it would be difficult to consider a patient with this level of albumin well nourished. Five of these six were hypoglycemic.

In two of the patients a clinical diagnosis of alcoholic pancreatitis was made during the admission for hypothermia. One of these was hyperglycemic (case 1) and one hypoglycemic (case 10). In one patient with insulin-requiring diabetes

TABLE 1.—*Serum and Urine Glucose in Twenty-two Hypothermic Patients*

Case	*Age*	*Sex*	*Temp. F°*	*Diagnosis*	*Serum Glucose mg/dl*	*Urine Glucose (Dipstick)*	*Outcome*
1. ..	51	M	84	ETOH, seizure, pancreatitis, GI bleeding, profound folate deficiency (hematocrit = 10%)	157	(−)	Died
2. ..	39	M	87.6	ETOH, seizure, chronic pancreatitis, sepsis, shock, renal failure, arrest	317	2+	Died
3. ..	62	M	80	ETOH, urinary tract infection, hypoxia	85	(−)	Alive
4. ..	55	M	82	ETOH, parietal fracture, epidural hematoma, SIADH	110	(−)	Alive
5. ..	80	M	93	ETOH, ketosis	200	(−)	Alive
6. ..	58	M	85	ETOH, cirrhosis, ascites, liver failure, DIC, cardiopulmonary arrest	76	1+	Died
7. ..	85	M	95	Cancer pancreas, diabetes, respiratory arrest	25	(−)	Died
8. ..	62	M	86	ETOH, Gram-negative sepsis, hypothyroidism	26	(−)	Alive
9. ..	70	M	92	ETOH, hypertension	42	(−)	Alive
10. ..	53	M	92	ETOH, cirrhosis, anemia, GI bleeding, pancreatitis, cardiac arrest	37	(−)	Alive
11. ..	65	M	83	ETOH, Gram-negative sepsis, ATN, pulmonary edema, GI bleeding	13	(−)	Died
12. ..	74	M	88	ETOH, cancer prostate, dementia, GI bleeding	102	(−)	Alive
13. ..	67	M	85	ETOH, Gram-negative sepsis, hypotension	47	(−)	Alive
14. ..	55	M	90	Myxedema, pneumonia	175	(−)	Alive
15. ..	70	F	75	ETOH, ATN, pneumonia	18	2+	Alive
16. ..	68	M	92	ETOH, cirrhosis, hepatoma	112	(−)	Died
17. ..	50+	F	87	ETOH, cirrhosis, ascites	90	(−)	Alive
18. ..	68	M	84	ETOH, dementia, hypothyroidism	40	(−)	Alive
19. ..	62	F	89	ETOH, Gram-negative pneumonia	95	(−)	Alive
20. ..	50+	M	91	ETOH, Wernicke-Korsakoff encephalopathy	175	(−)	Alive
21. ..	59	M	84	ETOH, sepsis, pneumonia	128	(−)	Alive
22. ..	59	M	86	ETOH, Gram-negative sepsis, ATN	35	(−)	Died

ATN = acute tubular necrosis
GI = gastrointestinal
DIC = disseminated intravascular coagulation
SIADH = syndrome of inappropriate antidiuretic hormone
ETOH = alcohol use or alcoholism

and pancreatic carcinoma the serum glucose value was 25 mg per dl (case 7). No other patient was known to have diabetes. Of four patients with cirrhosis of the liver listed as an admission diagnosis, only one was hypoglycemic (case 10), and he had concurrent pancreatitis.

Of the nine hypoglycemic patients, four died (44 percent). There were also four deaths among the remaining 13 patients with serum glucose levels greater than 50 mg per dl.

A listing of admission data, diagnoses, glucose values and outcome is given in Table 1.

Discussion

As may be seen in Table 1, the multiplicity of problems seen in this small series of patients prohibits making valid inferences about the influence of hypoglycemia on morbidity or mortality. It was supposed that some of our hypothermic patients might be hypoglycemic, drawn as they were from a population predisposed to hypoglycemia: malnourished[32,33] alcoholic persons.[29-31] But the fact that 41 percent of our patients were hypoglycemic made this a surprisingly common finding in alcoholic accidental hypothermia. In a study by Weyman and his colleagues[24] of 39 cases of hypothermia—82 percent of which had alcohol listed as a predisposing factor—in only one was the serum glucose level below 50 mg per dl. In our series there was no reliable relationship between depth of hypothermia and serum glucose levels.

In light of these data, all hypothermic patients, unless serum glucose values are known to be normal or high, should receive 50 percent glucose solution intravenously immediately after a serum specimen has been drawn for glucose measurement. Because of hypothermic renal tubular glycosuria, the presence of glucose in the urine of cold patients is no guarantee of elevated levels of serum glucose, and may indeed be contributing to the hypoglycemia of hypothermia.

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Intraspinal Tumors in Children

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Thirty cases of intraspinal neoplasms occurring during the first two decades of life are reviewed. Histologic examination showed 13 of these to be astrocytomas, 6 neuroblastomas, 5 sarcomas, 3 ependymomas, 2 neurofibromas and 1 a schwannoma. Orthopedic deformities developed or worsened in 60 percent of patients surviving longer than a year after diagnosis. In five patients some form of endocrine deficiency developed after irradiation. For treatment of radiosensitive extradural malignant lesions, biopsy followed by irradiation is advocated.

SPINAL CORD TUMORS occur rarely in children but present formidable problems to neurosurgeons, orthopedists and pediatricians. Frequently, there is an error or a significant delay in diagnosis; this is often related to the association of the onset of symptoms with minor illnesses or trauma.[1-9] Morbidity is related not only to the region of the spinal cord involved and the tumor type, but also to the child's often adverse response to the treatment modalities.[7,8,10-17] Extradural malignant lesions and the intrinsic gliomas predominate in the pediatric age group, whereas in adults schwannomas and meningiomas constitute the most frequent intraspinal tumors.[1,5,7,18] The ratio of intracranial to intraspinal tumors reported in the literature varies from 20:1 to 5:1 for children—in contrast to the commonly reported 5:1 ratio for adults.[1-4,9,18,19]

Clinical Data

Between 1945 and 1978 there were 30 patients treated at the University of California, San Francisco, for intraspinal neoplasms diagnosed during the first two decades of life. Excluded from this series are patients in whom operations were not carried out and those with vascular malformations, spinal metastatic lesions from previously manifested malignant conditions and tumors associated with developmental anomalies of the bony spinal canal.

Patients ranged in age from 2 months to 17 years, averaging 8.0 years; half were younger than 7 years. Of these patients, 17 were boys and 13 were girls. Predictably, boys predominated among the patients with neuroblastomas (5:1) and astrocytomas (8:5).[20,21] Twelve tumors were thoracolumbar, eight cervical, five thoracic, three cervicothoracic, and two lumbosacral. The tumors are categorized by type and location in Table 1.

The distribution of tumor types in this series is —allowing for differences in selection criteria— quite similar to that found in other series (Table 2). It is notable, however, that in our series gliomas account for 53 percent of the tumors, which is significantly higher than their incidence in any other series and more than double their incidence in all series combined.

We found no epidermoid/dermoid or lipoma without an associated anomaly of the vertebral canal. Consistent with the observations of others

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computerized tomography

TABLE 1.—*Tumor Location and Type, in Order of Frequency*

Location	*Type*	*Number of Cases*
Intramedullary	Astrocytomas/ mixed gliomas	13
Extradural	Neuroblastomas	6
	Sarcomas	4
	Neurofibromas	2
Intradural extramedullary	Ependymomas	3
	Schwannoma	1
Both intradural and extradural	Sarcoma	1
TOTAL		30

are our findings of a slight male predominance and a clustering of tumor occurrence in children under 2 years old and in those near 13 years.*

Symptoms, Signs and Diagnosis

The duration of symptoms before a correct diagnosis was made ranged from three weeks to four years, averaging ten months. For the extradural malignant lesions, the average duration from onset of symptoms until diagnosis was 4.5 months, as compared with 2 months for ependymomas, 15 months for astrocytomas and 2 years for neurofibromas. At least six cases (20 percent) were initially diagnosed incorrectly, with the patients' symptoms attributed in three instances to previous minor trauma.

The initial symptoms are summarized in Table 3. Whereas the most frequent complaint, pain, was about equally frequent with extradural and with intramedullary lesions, there were striking differences in the motor symptomatology between these groups: all five cases of early paraparesis and all three of sphincter disturbance occurred with extradural tumors; and with intramedullary tumors, weakness was manifested as quadriparesis, hemiparesis or monoparesis. Torticollis and scoliosis occurred exclusively with astrocytomas.

The physical signs are summarized in Table 4. Most frequently found was weakness, usually manifested as an abnormality in gait. Next most frequent were sensory changes and next were abnormalities in deep tendon reflexes.

Values of cerebrospinal fluid (CSF) protein,

*1, 2, 4, 5, 7, 9, 13, 19, 22-25

TABLE 2.—*Incidence of Spinal Cord Tumors in Children—From the Literature and in the Present Series*

Tumor Type	*Hamby 1944* Number (percent)	*Anderson & Carson 1953* Number (percent)	*Ross & Bailey 1953* Number (percent)	*Svien et al 1954* Number (percent)	*Grant & Austin 1956* Number (percent)	*Haft et al 1959* Number (percent)	*Rand & Rand 1960* Number (percent)	*Matson 1969* Number (percent)	*Banna & Gryspeet 1971* Number (percent)	*Till 1975* Number (percent)	*Fraser et al 1977* Number (percent)	*Giuffre & Di Lorenzo 1977* Number (percent)	*Boggan et al 1978* Number (percent)	*Total* Number (percent)
Gliomas	44(21)	9(43)	.....	.....	.....	.....	.....	.....	9(28)	.....	4(10)	.....	.....	187(24.3)
Astrocytomas	.....	.....	4(30)	2(5)	3(10)	3(10)	9(14)	24(18)	.....	2(3)	.....	7(13)	13(43)	.....
Ependymomas	.....	.....	1(8)	4(10)	3(10)	1(3)	8(12)	6(4)	.....	4(6)	.....	1(2)	3(10)	.....
Glioblastoma	.....	.....	.....	.....	1(3)	.....	.....	.....	.....	.....	.....	.....	.....	.....
Unclassified	.....	.....	.....	2(5)	.....	5(17)	3(5)	.....	.....	10(15)	.....	2(4)	.....	.....
Medulloblastomas	.....	.....	.....	.....	.....	.....	4(6)	4(3)	6(19)	1(1)	.....	.....	.....	15(1.9)
Meningiomas	10(5)	.....	1(8)	.....	5(17)	1(3)	2(3)	3(2)	.....	2(3)	1(2)	.....	.....	25(3.2)
Neurofibromas	23(11)	3(14)	1(8)	8(20)	3(3)	2(7)	5(8)	6(4)	2(6)	6(9)	.....	3(6)	2(7)	64(8.3)
Sarcomas	42(20)	3(14)	2(15)	5(12)	5(17)	4(13)	12(18)	18(13)	4(12)	5(7)	3(8)	7(13)	5(17)	115(14.9)
Lymphomas	9(4)	.....	.....	2(5)	1(3)	.....	.....	.....	.....	.....	2(5)	.....	.....	14(1.8)
Carcinomas	.....	.....	.....	2(5)	.....	.....	.....	.....	.....	.....	1(2)	.....	.....	3(0.4)
Neuroblastomas	6(3)	2(10)	.....	.....	2(7)	6(20)	5(8)	24(18)	8(25)	17(25)	11(28)	14(26)	6(20)	101(13.1)
Ganglioneuromas	.....	.....	.....	.....	1(3)	3(10)	1(1)	3(2)	.....	1(1)	.....	1(2)	.....	10(1.3)
Lipomas	10(5)	.....	1(8)	6(15)	.....	.....	4(6)	7(5)	.....	.....	.....	.....	.....	28(3.6)
Epidermoids or dermoids	37(17)	.....	.....	.....	.....	4(13)	2(3)	14(10)	.....	3(4)	4(10)	4(8)	.....	68(8.9)
Teratomas	.....	.....	2(15)	.....	.....	.....	1(1)	13(10)	.....	1(1)	.....	2(4)	.....	19(2.5)
Blood vessel tumors	7(3)	3(14)	1(8)	3(7)	1(3)	1(3)	2(3)	3(2)	1(3)	1(1)	1(2)	.....	.....	24(3.1)
Others	26(12)	1(5)	.....	7(17)	5(17)	.....	7(11)	9(7)	2(6)	15(22)	13(32)	12(23)	1(3)	98(12.7)
TOTALS	214	21	13	41	30	30	65	134	32	68	40	53	30	771

which was determined in 20 patients, ranged from 24 to 5,400 mg per dl, averaging 750 mg per dl. In only one patient (in whom the tumor was an extradural neurofibroma) was there a normal level of CSF protein; in 12 patients it exceeded 100 mg per dl and in four of these it was more than 1,000 mg per dl. The CSF protein level tended to be lower in the patients with intramedullary tumors, although there were notable exceptions.

CSF cytology was positive for malignant cells in two patients with ependymomas and one with an undifferentiated sarcoma having an intradural subarachnoid component.

Plain x-ray films were reviewed in 26 cases, in 10 of which no abnormalities were noted. The preoperative findings are summarized in Table 5. It is notable that five of seven patients with pedicle erosion had extradural tumors, whereas only one of the extradural lesions was associated with radiologically observed scoliosis. An increased interpediculate space was observed in four patients with astrocytomas and two with neurofibromas.

Myelography provided a definitive diagnosis in each of the 29 cases in which it was done, and in 16 patients a complete block was found. Air myelography with tomography was carried out in four cases, primarily to evaluate possible communicating cystic enlargement of the spinal cord, which was not found in this series. Computerized tomography (CT) showed a paraspinous mass in two cases and vertebral body sclerosis in another. Our recent experience suggests that CT scanning utilizing computer reconstruction into sagittal and coronal planes, magnification modes and concomitant metrizamide (Amipaque) myelography should be useful in the evaluation of intradural abnormalities. The radioisotope bone scan was positive in only one of five cases, a patient with Ewing sarcoma who also had vertebral body sclerosis observable on plain x-ray films and CT scan.

TABLE 3.—*Initial Symptoms in Order of Frequency (30 Cases)*

Symptom	*Occurrences*
Pain	
Local	14
Radicular	6
Weakness	
Paraparesis	5
Monoparesis	4
Quadriparesis	2
Hemiparesis	2
Sphincter disturbance	3
Torticollis and/or scoliosis	3
Hydrocephalus	1
Neck mass	1

TABLE 4.—*Physical Findings in Order of Frequency (30 Cases)*

Sign	*Occurrences*
Paresis	
Paraparesis	9
Monoparesis	6
Hemiparesis	2
Quadriparesis	2
Hypalgesia	
Sensory loss	10
Radicular loss	3
Patchy loss	3
Deep tendon reflex abnormality	
Hyperactive	7
Hypoactive	6
Paraspinous mass	6
Scoliosis	6
Muscle atrophy	5
Sphincter disturbance	5
Vasomotor changes	1
Horner syndrome	1

TABLE 5—*Preoperative X-ray Findings in Order of Frequency (26 Cases)*

Finding	*Occurrences*
Normal	10
Scoliosis	7
Pedicle erosion	7
Interpediculate space or canal widening	6
Soft tissue mass with calcifications	2
Chest x-ray abnormality	2
Compression fracture	1
Disk space narrowing	1
Vertebral scalloping	1
Vertebral body sclerosis	1

Pathology and Survival

Astrocytomas

Eight boys and five girls had astrocytomas. Eleven were well differentiated astrocytomas, four of them cystic; and two patients had mixed gliomas, one of which had anaplastic histologic features. The cystic tumors involved more of the spinal cord, averaging 7.5 vertebral segments as compared with an average of 3.5 segments in the cases with solid tumors. Patients with cystic tumors seemed to respond better to treatment, even when there was cervical involvement. All but one of the astrocytomas were completely intramedullary.

Eleven patients received surgical operations and irradiation, and two had surgical treatment alone. Two patients received chemotherapy in addition

to irradiation and surgical operation, without observed benefit. Two patients had local reoperations. One of these was a cordectomy to excise the remaining tumor and relieve severe paraplegic flexor spasms and chronic pain. Seven patients have survived: five male and two female. Five have been followed longer than two years, with an average survival of 7.9 years. Two of the seven survivors are fully active without clinical evidence of disease and two have minor gait problems; the patient in whom cordectomy was done is paraplegic. One of the two survivors followed less than two years has no evidence of disease; the other has a progressive paraparesis. The six patients who died of tumor progression had cervical lesions, and survived an average of six years after operation (ranging from five months to 14 years). In two patients with cervical lesions, hypothyroidism developed after surgical operation and irradiation.

Neuroblastomas

Five boys and one girl had neuroblastomas, all extradural. Three of the six had palpable paraspinous masses; in one case, a biopsy of the mass constituted the patient's operation. All of the patients were treated postoperatively with irradiation in an average dose of 4,070 rads. Three patients died. Their average duration of postoperative survival was 1.6 years. Death was caused by visceral and pulmonary metastasis, with the spinal canal free of disease. In the survivors (3 months, 1 year and 19 years since diagnosis) diagnoses were made before they attained 1 year of age, as is frequently the case with long-term survivors having neuroblastomas.[7,20,26] Elevated urinary excretion of catecholamine metabolites was found inconsistently. Showing the presence by electron microscopy of intracytoplasmic secretory granules in an undifferentated tumor of small round-cells was reliable for diagnosis.

Sarcomas

Two boys and three girls had sarcomas. Three of these tumors were undifferentiated, one was a Ewing sarcoma and one was a rhabdomyosarcoma. In the only survivor among these patients, a girl with Ewing sarcoma, the duration of follow-up is less than two years. In this patient a second exploration was done for presumed recurrence, which proved to be an epiduritis probably due to irradiation; such an occurrence has been reported by Giuffre.[19] The average duration of survival for the other four patients was 1.5 years, ranging from 6 months to 3 years, 10 months. One of these patients died of a pneumocystic pulmonary infection one year and two months after operation; the metastatic tumors in this patient had responded well to chemotherapy and there was no evidence of spinal tumor at autopsy. The other three patients died of visceral metastatic lesions, and one had cerebral metastatic spread as well. The patients with sarcomas received an average of 3,750 rads of irradiation postoperatively, and two patients also received chemotherapy.

Ependymomas and Ependymoblastoma

Two girls had ependymomas and one an ependymoblastoma in the region of the conus and cauda equina. One patient received only surgical treatment and has survived 16.5 years without evidence of disease. The other two have survived 2.7 and 9.0 years postoperatively. One patient had cerebral metastatic lesions, which were verified by operation, and two intraspinal recurrences; the metastatic lesions responded well to a second course of radiation therapy and chemotherapy with BCNU (1,3-bis[2-chloroethyl]-1-nitrosurea). In this patient evidence of hypopituitarism developed—as it did in the patient with ependymoblastoma who received neuroaxis irradiation.

Neurofibromas and Schwannoma

Two patients had neurofibromas, and one a schwannoma. The three patients with these tumors have done well, having survived three, eight and ten years without recurrent symptoms or evidence of progression even though the tumors were only partly excised (and the residual tumors irradiated).

Treatment

Surgical Therapy

Laminectomies were done in 28 patients, and a three-level hemilaminectomy in one. In one patient only a biopsy study of a paraspinous mass was done. There were no perioperative deaths. The indications for surgical reexploration were development of a cyst, inadequate first biopsy, cordectomy, tumor metastasis within the spinal canal and arachnoiditis. In one patient who had an ependymoma, four laminectomies were carried out over nine years, involving a total of 18 vertebral levels. Some additional procedures done as part of the initial management of these patients

TABLE 6.—*Orthopedic Abnormalities (30 Cases)*

Finding	*Occurrences*
Preoperative	
Scoliosis	7
Increased lumbar lordosis	2
Shorter extremity	1
Valgus ankle deformity	1
Postoperative	
Kyphoscoliosis	9
Scoliosis	6
Kyphosis	2
Contractures	2
Increased lumbar lordosis	1
Equinovarus ankle deformity	1

were lumboperitoneal shunting, thoractomy and cutaneous removal of a neurofibroma.

Radiation Therapy and Chemotherapy

Twenty-six patients in whom resections were incomplete were treated with postoperative irradiation of at least 1,000 rads tumor dose, usually given through a single posterior portal.[27] Irradiation, in an average total dose of 4,000 rads per patient, was used in treating 11 of the astrocytomas, all of the neuroblastomas and sarcomas, 2 of the 3 ependymomas, 1 neurofibroma and the schwannoma. The patient with ependymoblastoma and one patient with ependymoma, in whom cerebral metastatic lesions developed, received whole-brain irradiation as well, and the latter also received local irradiation of metastatic recurrences within the canal.

Hypopituitarism has developed in two patients. Following head irradiation, as in these cases, hypopituitarism is a recognized complication that can often be prevented by proper shielding.[15] In three patients evidence of hypothyroidism has been noted. All three had cervical tumors and received incidental radiation to the thyroid area.

Eight patients received various chemotherapeutic regimens. There was no consistent response of any tumor type to chemotherapy, although BCNU has been found quite effective against ependymomas (personal communication of Drs. Victor Levin and Charles B. Wilson, Brain Tumor Research Center, University of California, San Francisco). Chemotherapy in combination with surgical and radiation therapy has not been found better than just surgical and radiation therapy in the initial management of neuroblastoma; and the use of adjuvant chemotherapy is now reserved for disseminated disease or recurrences.[28]

Orthopedic Aspects

In 60 percent of those patients surviving longer than a year, either a new orthopedic abnormality developed or significant structural worsening occurred following treatment of their tumor. The radiologically verified preoperative and postoperative postural abnormalities observed are summarized in Table 6. Orthopedic intervention was necessary in nine cases. Of the nine patients with preoperative postural abnormalities, only one did not progress postoperatively. Of our 15 patients with postoperative abnormalities, 13 also received postoperative irradiation. In four patients, bracing or body casts were necessary; in three, tendon releases were required; in one, an anterior cervical fusion was done, which improved and arrested progression of her cervical kyphosis; and in another a severe swan-neck deformity later developed after the patient decided against surgical fusion. In two patients only moderate scoliosis developed, although one had a three-level hemilaminectomy (vertebrae T-12 through L-2) and received postoperative irradiation, and the other had four laminectomies involving a total of 18 levels, as well as radiation therapy. There was no correlation between the severity of the orthopedic deformity and either the number of vertebral segments involved at operation or the patient's age at the time of treatment. However, as Fraser and associates also found, the higher the spinal level of the laminectomy, the more severe the deformity tended to be.[13]

As noted by Boldrey and co-workers,[29] orthopedic deformity—most frequently scoliosis[2,7,25]—may be the presenting sign of a childhood spinal cord tumor. Moreover, in approximately half of all children undergoing laminectomy as a result of a spinal cord tumor, a postoperative spinal deformity develops, most frequently kyphosis or kyphoscoliosis.[5,7,8,11-13,30] The cause of these deformities remains unclear, although surgical procedures, irradiation, arachnoiditis and neuromuscular imbalances have each been implicated.[8,11,16,31-35] The patient's age, the dose and field of irradiation, the extent of surgical operation, and the location of the tumor each has variable effects on the severity of the deformity.[11,13,16,31,35]

The normal configuration of the spine results from the interaction of dynamic growth and the effect of neuromuscular and gravitational forces on spinal structures.[11,30,33,36] Any of these factors

may be affected by the tumor directly or by surgical intervention or irradiation. Surgical intervention is probably the most important factor because it can destroy the critical stabilizing elements of the spine.[7,8,11,13,30,33] When wide exposure of the canal is necessary, the technique of laminotomy and reconstruction recently described by Raimondi[14] lessens the extent of surgical interference with the normal dynamic forces and stabilizing elements of the spine. An important aspect of this treatment regimen is the provision of early bracing, orthopedic attention and physical therapy. In patients with malignant extradural lesions, the use of microsurgical biopsy may diminish the role of surgical procedures in producing postoperative spinal deformity.

Discussion

The frequent misdiagnosis of childhood spinal cord tumors emphasizes the need for suspicion when examining any child with a gait disorder, back or leg pain, focal weakness, postural abnormalities or loss of acquired sphincter control. Weakness and pain are the most common symptoms; and motor, sensory and reflex changes are the most frequent physical findings.[1,4,5,7,9,13,24] The diagnostic approach must be aggressive. Complete plain x-ray films of the spine should be made because the symptoms of cervical or thoracic tumors are not infrequently confined initially to the low back or lower extremities; and in approximately 60 percent of cases of spinal tumor, close scrutiny will show pathologic radiographic changes. Contrast myelography is the diagnostic procedure of choice. The use of CT scanning is increasing.

The role of surgical procedures in the treatment of malignant extradural spinal cord tumors of childhood can reasonably be confined to decompressive laminectomy for tissue diagnosis, followed by irradiation. One can seldom achieve a total resection of these tumors, whereas they are generally radiosensitive.[16,18,20,26,37] Orthopedic abnormalities that frequently develop following treatment are in part related to surgical resection of bony and musculotendinous spinal components.[7,8,11-13,30] Recent advances in microsurgical technique reduce the need for extensive laminectomy when taking biopsy specimens of extradural lesions.[38] Other considerations supporting this approach are that the location and extent of the tumor can be well determined by computerized tomography or myelography (or both), that these patients usually die of visceral metastatic lesions with the spinal canal free of gross tumor, and that newer chemotherapeutic agents are achieving a greater response in these neoplasms.[26,28,37,39] These considerations are supported by the reported results of Gilbert and co-workers, Rubin and associates and others treating metastatic spinal cord compression in children and adults without surgical intervention.[37,40-43]

The surgical management of intradural spinal neoplasms still requires either laminectomy or laminotomy with reconstruction—as is also true for epidural lesions that progress rapidly or progress during irradiation. In the cases with lower cervical astrocytomas, an aggressive microneurosurgical approach (as employed by Malis[44] and by Garrido and Stein[45] in treating intramedullary tumors), when combined with irradiation and chemotherapy, might improve the length and the quality of life for the patient (though this view is not verified by the results in this series or review of the literature).

With recent improvements in radiotherapy and advances in chemotherapy, the prognosis for patients with epidural malignant lesions is improving.[26,28,37,39,40,42,43] Microsurgical biopsy and irradiation of these lesions probably will replace wide laminectomy except when compression of the spinal cord is proceeding precipitously. In metastatic compression of the spinal cord in adults irradiation without surgical intervention has become the primary treatment protocol for radiosensitive tumors when the type of primary tumor is known.[40,41] This approach has been effective in the management of certain spinal neoplasms in children as well.[37,42,43]

The cases of extradural malignant lesions had the worst prognosis in our study; and when they were fatal, patients' survival after diagnosis averaged less than two years. Patients with gliomas, except those in the cervical region, did well with treatment. Even patients with cervical astrocytomas survived an average of six years following treatment. With all tumor types, spinal cord function was sufficient to allow most survivors a good quality of life if treatment was initiated early and the posttreatment orthopedic and medical problems were properly managed.

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Antimicrobial Agent-Associated Colitis and Diarrhea

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Although antimicrobial agent-associated colitis has been recognized as a clinicopathologic entity for years, the cause of this disease has been determined only recently. Virtually all cases of pseudomembranous colitis and some cases of antimicrobial agent-associated nonspecific colitis or diarrhea have been shown to be caused by a toxin of Clostridium difficile. *Methods for cultivating* C difficile *from feces and for detecting the toxin have been developed. Oral administration of vancomycin has proved to be effective for the treatment of* C difficile*-induced colitis, although isolated instances of relapse after treatment have been documented.*

The discovery of C difficile *as a human intestinal pathogen has provided an explanation for some, but not all cases of antimicrobial agent-associated diarrhea. The epidemiology, pathogenesis and means of prevention of* C difficile *toxin-induced diarrhea remain to be determined.*

ALTHOUGH GASTROINTESTINAL SIDE EFFECTS are probably the most common adverse effects of antimicrobial therapy, the cause of the most serious of these, pseudomembranous colitis, has only recently been elucidated. Bartlett and coworkers[1] and Rifkin and colleagues[2] discovered that a toxin produced by *Clostridium difficile* was the cause of ileocecitis in hamsters given clindamycin. Techniques developed during study of this hamster model have been applied to antimicrobial agent-associated diarrhea in humans, with impressive results. *C difficile* toxin has been shown to be the cause of virtually all cases of pseudomembranous colitis.[3-7] In addition, some cases of antimicrobial agent-associated diarrhea (in which a pseudomembrane is not present) appear to be caused by this toxin.[3,6] These diseases are unique in that an organism which may normally be found in the human colon, causes illness only after administration of antimicrobial agents.

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Terminology

A great deal of confusion surrounds pseudomembranous and antimicrobial-associated diseases

of the gut. Pseudomembranous *entero*colitis is an entity, first described in the preantibiotic era,[8] in which a gastrointestinal operation or hypotension was a common if not essential substratum. Diarrhea occurred in less than half of the patients, involvement of the gastrointestinal tract was usually most prominent in the small bowel and death was common.[9] During the 1950's and 1960's, the same or a similar disease was attributed to overgrowth in the bowel of enterotoxin-producing *Staphylococcus aureus,* presumably as a sequela of antimicrobial therapy. Formation of gastrointestinal pseudomembrane has also been attributed to leukemia, heavy metal intoxication, bowel obstruction, cardiac disease and uremia.[9] Gorbach and Bartlett question whether either *S aureus* or antimicrobial therapy should be considered as possible causes of pseudomembranous *entero*colitis.[9] Retrospective analysis of such cases is fraught with problems because of variable and often inadequate criteria for diagnosis. Antimicrobial agent-associated (pseudomembranous) colitis does not involve the small bowel, and should be considered as an entity distinct from pseudomembranous *entero*colitis and staphylococcal colitis.

Results of sigmoidoscopy in combination with rectal biopsy have been used to categorize antimicrobial agent-associated diarrhea as pseudomembranous colitis, nonspecific colitis and diarrhea without colitis.[10-12] Several problems are inherent in this type of classification. Sumner and Tedesco[12] have documented the progression of nonspecific antimicrobial-associated colitis to pseudomembranous colitis. It is likely that in such patients diarrhea developed first, then nonspecific colitis and, finally, pseudomembranous colitis.

Volpicelli and co-workers[13] and others[14,15] have described sparing of the rectosigmoid colon in patients with antimicrobial agent-associated colitis of the right side. Unfortunately, neither *C difficile* nor its toxin was sought in any of these cases. Tedesco[16] has recently reported five cases of patients with toxin-positive pseudomembranous colitis as documented by colonoscopy; in each instance results of sigmoidoscopy were negative. Thus, the limitations of a disease classification based on sigmoidoscopic findings are evident—gross and microscopic pathological findings may change significantly over several days, and may also vary from segment to segment of the colon. Because therapeutic considerations are based on the presence of toxin in feces as well as pseudomembrane or plaque formation, *Clostridium difficile*-induced colitis (or diarrhea) may be a more appropriate term.

Clostridium difficile-Induced Ileocecitis in Hamsters

Small,[17] in 1968, described the consistent development of a fatal ileocecitis in Syrian hamsters after administration of lincomycin. Green[18] noted that material taken from hamsters or guinea pigs dying of penicillin-induced ileocecitis produced a cytopathic effect in WI-38 cells, and concluded that a latent virus was responsible. Other investigators later found that a single dose of clindamycin (as well as a variety of other antimicrobial agents) would also cause ileocecitis[19-22]; disease was either prevented or postponed when vancomycin was given orally around the time of the clindamycin challenge.[23,24] A transmissible agent was implicated when Bartlett and colleagues[1] found that serial passage of cecal contents from diseased to healthy untreated hamsters consistently caused ileocecitis in the recipient; assay of cecal contents for clindamycin was negative after the first two or three passages. When the cecal contents from a hamster dying of ileocecitis were filtered (to remove bacteria and viruses) and then injected intracecally into a healthy animal, ileocecitis still developed in the recipient.[1] However, if the cecal contents were heated[25] or incubated with polyvalent gas gangrene antitoxin before injection,[1] ileocecitis did not develop in the recipient. Thus, hamster ileocecitis was found to be a disease that could be prevented by vancomycin administration and that was caused by a transmissible agent.

The filtration studies and the finding that ileocecitis could be prevented by heating or incubating cecal contents with gas gangrene antitoxin suggested that a toxin, probably of clostridial origin, was involved. Subsequent studies showed that this toxin was produced by *Clostridium difficile*.[1,3,26] This elegant series of experiments satisfied Koch's postulates for disease due to a transmissible agent. A less cumbersome and more rapid means of toxin detection was developed when it was noted that *C difficile* toxin produces a cytopathic effect in tissue culture.[3,25-31] This cytopathic effect is probably the same as that detected by Green in hamsters and guinea pigs dying of penicillin-induced ileocecitis.[18] Detection of *C difficile* toxin in feces by cell culture assay has been used

extensively to study antimicrobial-associated diarrhea in humans.[3-7,10,16,26]

Sources of *Clostridium difficile*

C difficile has been isolated from a variety of sources. The organism was first described and named *Bacillus difficilis* in 1935 by Hall and O'Toole, who recovered it from the feces of four of ten healthy newborn infants.[32] In 1940 Snyder reported the isolation of *B difficilis* from the feces of 10 of 22 healthy infants during the first year of life.[33] Several other studies have confirmed the presence of *C difficile* in the feces of asymptomatic infants.[34-36]

In contrast, *C difficile* was isolated from the feces of only 4 of 137 patients undergoing detailed fecal flora studies.[37] The low incidence of carriage in this study may have been due to the extremely complex fecal flora of adults and to the lack of a highly selective medium for *C difficile* at the time the study was done.

C difficile was also isolated from the urogenital tract of 100 percent of men suffering nonspecific urethritis and from 72 percent of women attending a venereal disease clinic.[38] This latter finding suggests that newborn infants may become colonized during passage through the birth canal.

C *difficile* has been isolated on rare occasions from blood,[39,40] pleural fluid,[39] peritoneal fluid[39] and soft tissue infection (usually related to surgical operations of the bowel).[29,30,40] Smith and King[39] were unable to attribute definite pathological significance to the recovery of *C difficile* in such instances.

Reports of isolation of *C difficile* from the environment are limited. Hafiz and Oakley[34] recovered the organism from sand, soil and mud (as well as from donkey, horse and camel dung). The only hospital environmental isolation of *C difficile* was reported by Keighley and co-workers,[41] who recovered it once from a shelf on which bedpans were stored. In the latter instance, "repeated searches in the ward environment" were made because of continual occurrence of *C difficile* colitis on a surgical ward. Contamination of the hospital environment could explain the reported clustering of cases of colitis.[6,42] The isolation of *C difficile* from soil and feces of domesticated animals suggests that contamination of food (vegetables by soil and animal carcasses by feces during slaughter) is another potential source for infection of the human gut.

Pathogenesis

Agents reported to have caused pseudomembranous colitis are invariably present in feces, often in a very high concentration.[43] These agents may alter the normal gut flora so as to render it incapable of suppressing growth or toxin elaboration by *C difficile*. The mechanism by which the normal flora might prevent the proliferation of *C difficile* is not known; however, competition for mucosal attachment sites, production of chemical inhibitors, or use of nutrients essential for growth of *C difficile* have been postulated.[29,37] Once *C difficile* becomes established in the gut of a "susceptible" patient it may proliferate to achieve high counts and elaborate quantities of toxin sufficient to cause colonic mucosal injury. Reports of colitis developing up to three weeks after the inciting antimicrobial agent has been discontinued suggest that the intestinal microflora may not be reconstituted for some time.[44] Diarrhea has not developed in all adult patients with high fecal counts of *C difficile*[29,45] (an observation also made by W. L. George, M. E. Mulligan and S. M. Finegold, unpublished data, 1979) nor has it occurred in all infants or adults with *C difficile* and toxin in their feces.[36,45,46] Therefore, other factors such as host susceptibility to the effects of toxin must be important.

Clostridium difficile Toxin

The toxin of *C difficile* has been purified and partially characterized by several different groups of investigators who have reported molecular weights of approximately 107,000, 240,000 and 550,000 daltons.[28,47-50] Treatment of the 550,000 dalton moiety with strong reducing agents yields 50,000 dalton polypeptide chains; thus, the various molecular weights reported may represent differences in methods used for toxin purification. Inactivation of the toxin by amylase and proteolytic enzymes indicate that the toxin is a glycoprotein.[47] The toxin is present in the cytoplasm of the organism and is released upon bacterial cell lysis.[47] Controversy exists as to whether all strains of *C difficile* elaborate toxin[26,30,51]; apparent discrepancies in toxigenicity may simply reflect the various broth media employed and the varying nutritional requirements of different strains of *C difficile*. This latter possibility may be of relevance, however, because certain essential nutrients might be lacking in the human gut. It is clear, in

any case, that the vast majority of strains produce toxin. There is, however, considerable variability in the amount of toxin each produces.

The mechanism of action of the toxin is not known. Studies to date indicate that it causes a cytopathic effect in a variety of cell culture lines,[3,27,28,46-53] ileocecitis in hamsters,[10] and fluid accumulation in the isolated rabbit ileal loop assay[28] (but not in the suckling mouse assay[25]); it also increases vascular permeability in the rabbit dermis[47] and stimulates colonic guanylate cyclase in vitro.[52] Chang and co-workers[54] have recently shown that the toxin binds to the lipid portion of intracellular membranes. Adenyl cyclase, Na^+-K^+-ATPase and steroidogenesis in cell culture are not affected.[27,52]

In earlier studies, the cytopathic effect of feces from patients with colitis, and from hamsters with ileocecitis was found to be neutralized by the component of polyvalent gas gangrene antitoxin directed against *Clostridium sordellii* toxin. This finding initially led to suggestions that *C sordellii* was the cause of colitis.[5,55] Chang and co-workers[56] and others, however, have convincingly shown that neutralization of toxicity is an immunological cross-reaction between *C difficile* toxin and *C sordellii* antitoxin. *C sordellii* has not been shown to have any role in the development of colitis in humans or ileocecitis in hamsters.

Wilkins[52] has developed an antibody to the toxin of *C difficile*. If this antitoxin proves to be specific, then a simple immunological means for detecting toxin, such as gel diffusion, should be possible.

Pathology

Visualization of the colonic mucosa by sigmoidoscopy or colonoscopy may show adherent whitish-green or yellow, raised mucosal plaques[57,58]; the plaques may occasionally coalesce to form an extensive pseudomembrane. The intervening mucosa is typically erythematous, edematous and, occasionally, friable.[57,58] On microscopic examination, the well-formed pseudomembrane is seen to consist of mucin, fibrin, polymorphonuclear leukocytes and sloughed epithelial cells.[11,12,57] Microscopy of a rectal biopsy specimen in both pseudomembranous and nonspecific colitis will show infiltration of the lamina propria and, sometimes, submucosa, by acute or chronic inflammatory cells, or both, as well as focal necrosis of colonic epithelium (Figure 1). Dilatation of mucus-secreting glands is sometimes present, whereas crypt abscess, vasculitis and vascular thrombosis have not been noted.[11,12]

Involvement of the colon may be patchy, with sparing of the rectosigmoid segment.[13-16] Hence, previously reported cases of *C difficile*-induced diarrhea and nonspecific colitis may actually have been pseudomembranous colitis with rectal sparing.

Inciting Agents

Agents which have been reported to cause pseudomembranous colitis are shown in Table 1. Although lincomycin, clindamycin and ampicillin have been the most commonly reported causes of colitis, several recent reports have implicated various cephalosporins.[7,16,62-64] *C difficile* and its toxin have also been detected in the feces of one patient with diarrhea and another with nonspecific colitis in association with cefoxitin administration (L. George, M. Mulligan, and S. M. Finegold, unpublished data, 1979).

Antituberculous agents, urinary antiseptics (methenamine mandelate, nalidixic acid and nitro-

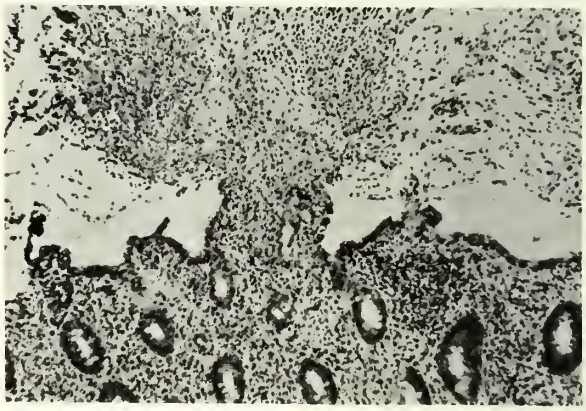

Figure 1.—Rectal biopsy specimen showing a plaque (superiorly) that is attached by stalk to the mucosa; inflammatory cell infiltrates are present in the lamina propria mucosae. (Reprinted by permission from Sumner & Tedesco[12]; copyright 1975, American Medical Association.)

TABLE 1.—*Agents Implicated as Causes of Colitis*

Penicillin[5,13-15,60]	Cefazolin[7,64]
Ampicillin[13,14,16,60,61]	Cefoxitin (see text)
Amoxicillin[13,14]	Tetracycline[60,61,66]
Nafcillin[7]	Chloramphenicol[7,66]
Lincomycin[61]	Metronidazole[61]
Clindamycin[44,60]	Cotrimoxazole[61,67]
Cephalexin[7,16,62,63]	Spiramycin[68]
Cephalothin[7,10,64]	Erythromycin[7]
	Aminoglycosides (orally given)[7,61]

furantoin) and aminoglycosides administered parenterally have not been implicated as causes of colitis.

Clinical Presentation

Diarrhea may develop at any time during, or up to three weeks following cessation of antimicrobial therapy; in occasional instances the onset of diarrhea may be as early as the second or third day of therapy.[44]

Typical symptoms and signs are watery diarrhea, nausea, vomiting, abdominal pain or cramps, low grade fever and leukocytosis.[44] In more severe cases, intense abdominal pain, high fever and pronounced leukocytosis may simulate acute intra-abdominal processes such as ruptured viscus, appendicitis or diverticulitis.[44] Protein-losing enteropathy, toxic megacolon, colonic perforation and shock are infrequent complications of antimicrobial agent-associated colitis.[44,69-73] Several deaths have been reported.

Bloody diarrhea may develop, particularly in association with penicillin or ampicillin therapy.

Figure 2.—Enlarged picture from an air-contrast barium enema study in a patient with pseudomembranous colitis; discrete, plaque-like lesions of the mucosa are evident. (Reprinted from Tedesco et al,[58] by permission from the *New England Journal of Medicine* 290:842, 1974.)

In such cases patients may have extensive mucosal erosions and inflammation of the proximal colon with relative or complete sparing of the rectosigmoid colon.[13-15]

Diagnosis

Definitive diagnosis in patients with antimicrobial agent-associated colitis requires the determination of extent and type of colonic pathological features, as well as of the causative agent and its toxin. *C difficile* colitis rarely, if ever, develops in the absence of antimicrobial therapy; therefore, a history of concurrent or recent antimicrobial therapy is essential. Gastrointestinal infection with *Campylobacter, Salmonella, Shigella, Yersinia* or *Entamoeba histolytica* may coincide with antimicrobial therapy and should be excluded by appropriate culture and microscopic examination. Pseudomembranous *entero*colitis must always be considered if the clinical features are consistent with that diagnosis. Gram-positive bacilli with subterminal spores and leukocytes may be present in the feces of patients with *C difficile* colitis or diarrhea, and these can be shown by Gram stain.

Most reported cases of pseudomembranous colitis have been documented by sigmoidoscopy. The recent reports of pseudomembranous disease of the proximal colon, with sparing of the rectosigmoid, indicate that negative results of a sigmoidoscopic examination do not exclude this diagnosis. In such cases a barium enema examination or colonoscopy should be done unless contraindicated. Although radiographic findings on barium enema have often been said to be nonspecific, Tedesco and colleagues[58] have suggested that a very specific pattern of plaque-like mucosal lesions may be detected, particularly if an air-contrast barium enema study is done (Figure 2). Acute onset of ulcerative colitis usually can be excluded by findings on barium enema and sigmoidoscopy, or colonoscopy with biopsy.

C difficile can be detected by use of a recently developed selective medium[59] in the feces of virtually all patients with pseudomembranous colitis, and in the feces of some patients with either antimicrobial agent-associated nonspecific colitis or diarrhea without colitis. However, *C difficile* has also been recovered frequently from the feces of healthy infants,[32-36] occasionally from feces of asymptomatic adults[37] and from the feces of a high percentage of asymptomatic adults who have received cefoxitin[45] (also noted by W. L. George, M. E. Mulligan and S. M. Finegold, unpublished

TABLE 2.—*Likelihood That* Clostridium difficile *Is Cause of Diarrhea*

	Pseudomembrane Detected and Restricted to Colon	*Nonspecific Colitis or Diarrhea Without Colitis*
Toxin test and culture for *C difficile* not done	Probable	Possible
Culture positive for *C difficile*	Extremely likely	Possible
Toxin test results and culture positive	Diagnostic	Likely

data, 1979). Hence, the recovery of this organism from feces is suggestive of but not diagnostic for *C difficile*-induced diarrhea.

The finding of a cytopathic effect produced by fecal filtrates in tissue culture, and neutralization of that effect by *C sordellii* antitoxin, is an appreciably more specific test and, as such, carries definite therapeutic implications.[5-7,60] However, the limited instances of this toxin in the feces of asymptomatic adults receiving antimicrobial therapy and of infants who do not have diarrhea should always be kept in mind.[36,45,46] When toxin is detected in the feces of a patient with either antimicrobial agent-associated nonspecific colitis, or diarrhea without colitis, it is likely, though not absolutely certain, that *C difficile* (toxin) is the cause of diarrhea. When both colonic pseudomembranes and toxin are detected, the diagnosis is definitely *C difficile* colitis[3-6,16,36,55,60] (Table 2).

The cause of toxin-negative nonspecific colitis or diarrhea has not been determined and certainly warrants investigation.

Therapy

The most important aspect of therapy for antimicrobial agent-associated colitis or diarrhea is discontinuation of the offending drug.[7,44] Symptoms and colonic pathological features in documented cases of pseudomembranous colitis will usually resolve within one to two weeks of discontinuation of therapy.[44] Ridding the gastrointestinal tract of the source of toxin, *C difficile,* is important in cases that do not improve after discontinuation of the offending drug. Vancomycin is highly effective against all strains of *C difficile* tested; when given orally in a dosage of 125 to 500 mg four times per day for seven to ten days, it produces rather prompt resolution of symptoms and disappearance of *C difficile* and toxin from the feces.[3,6,7,60] When vancomycin is given in a total daily dose of 500 mg, fecal levels average 351 ± 172 mg per gram.[6] Such values are at least 200-fold higher than the minimal inhibitory concentration of vancomycin for *C difficile.*[7,43]

Keighley and colleagues[6] have carried out a randomized double-blind study of the response of diarrhea in postoperative patients to vancomycin or placebo. In eight of nine patients with fecal toxin present, improvement or resolution of diarrhea occurred within five days of treatment with 125 mg of vancomycin four times per day. In only two of seven patients with fecal toxin in the placebo-treated group did improvement occur. When patients with diarrhea, but not toxin, were treated with placebo or vancomycin, the latter agent was not found to be efficacious. Data are insufficient to establish adequate guidelines for therapy for all cases of *C difficile* toxin-induced diarrhea. Certainly, when symptoms are protracted, or when a patient is very ill, vancomycin should be administered orally. Mildly symptomatic patients might be managed by discontinuation of the offending agent and administration of cholestyramine. If symptoms do not improve in several days, then cholestyramine should be discontinued and vancomycin, 125 mg four times per day, should be given. Fekety[7] has noted that the total cost of vancomycin is $175 to $280 when given in a dosage of two grams per day for seven days.

Although ototoxicity and nephrotoxicity may occur with parenteral administration of vancomycin, such toxicity has not been reported in association with oral therapy. Although vancomycin is normally poorly absorbed from the gastrointestinal tract, low levels have been detected in the sera of a few patients receiving treatment for colitis.[7,65] Because vancomycin is excreted by the kidney, renal function and, possibly, serum levels of the drug should be monitored if underlying renal dysfunction is present.

In a study published in 1979[74] relapse of *C difficile* toxin-induced colitis occurred in three patients. Neither the mechanism of relapse nor the frequency of relapse could be determined in these cases. Relapse in one patient responded to retreatment with vancomycin, and in another to cholestyramine therapy. The third patient's relapse responded to vancomycin retreatment, but a second and fatal relapse ensued after vancomycin was discontinued.

Metronidazole is also extremely active against *C difficile,* but the low levels achieved in the gut have been thought to limit its use for treatment of colitis. However, successful therapy of colitis

or diarrhea in six patients has recently been reported.[75-77] The rare cases of pseudomembranous colitis attributed to metronidazole therapy indicate that caution should be exercised regarding its use for therapy of colitis.

Cholestyramine has been shown to bind the toxin of *C difficile*[78,79] and, in theory, might be expected to be efficacious. Kreutzer and Milligan[80] reported response to cholestyramine in 12 patients with pseudomembranous colitis. The mean time to resolution of diarrhea was 2.1 days after beginning treatment with this drug. However, cholestyramine was given to four of the 12 patients within one to two days of onset of diarrhea; because antimicrobial agent-associated colitis is often self-limited, these four patients might have responded to discontinuation of the inciting antimicrobial agent without the addition of cholestyramine. Limited data presented at a workshop on clindamycin colitis indicated that there was response in 50 percent of patients treated with cholestyramine.[81] Cholestyramine will also bind vancomycin[79]; it would seem appropriate to avoid the simultaneous use of the two agents whenever possible.

Constipating agents, such as diphenoxylate hydrochloride (Lomotil) and opiate derivatives, have also been suggested as therapy for antimicrobial agent-associated colitis or diarrhea.[82] Some investigators have noted that the use of such agents appears to prolong, rather than ameliorate, symptoms and have suggested that they may predispose to toxic megacolon.[81,83,84] Data that document the efficacy of corticosteroid therapy are even more limited and there is certainly a theoretical hazard.

Vancomycin appears to be the agent of choice at this time for therapy of colitis or diarrhea due to *C difficile* toxin. Metronidazole, cholestyramine and, possibly, orally given bacitracin or other agents, as well as immunotherapy and inactivation of toxin by heavy metals,[47] may also prove to be of value. The variable and often self-limited course of *C difficile* toxin-induced diarrhea requires that therapeutic efficacy by evaluated in a controlled fashion.

Conclusion

The cause of pseudomembranous colitis and some other forms of antimicrobial agent-associated diarrhea has been established in the past several years. Laboratory techniques for diagnosis, although not widely available, now exist, and an effective form of therapy has been developed. Lest we become overconfident in our newly found knowledge, it should be noted that the epidemiology, pathogenesis and means of prevention of *C difficile* toxin-induced diarrhea remain obscure. The mechanism of action of the toxin has not been determined nor has a simple and rapid diagnostic test been developed. Moreover, the cause of toxin-negative antimicrobial-associated diarrhea remains unknown.

Addendum

Since preparation of this manuscript, several important papers regarding *C difficile* and diarrhea have been published. Members of the cephalosporin group of antimicrobials are undoubtedly a more frequent cause of *C difficile*-induced diarrhea than previously noted; Bartlett and colleagues[85] reported *C difficile*-induced pseudomembranous colitis in 17 patients who had been treated with a cephalosporin.

In regard to therapy of *C difficile*-induced diarrhea, orally given vancomycin was found to be effective therapy in a series of 79 patients.[86] Symptomatic relapse after discontinuation of vancomycin, however, occurred in 14 percent of cases treated; this finding underscores the need for careful follow-up of patients treated for colitis with vancomycin. Chang and co-workers[87] have shown resolution of *C difficile*-induced diarrhea in four patients treated with bacitracin given orally (relapse occurred in one of the four subjects, however). A review of therapy and prevention of *C difficile*-induced diarrhea has recently been published and guidelines for therapy formulated.[88] Mulligan and colleagues[89] have recently documented extensive hospital environmental contamination by *C difficile* in the vicinity of several patients with antimicrobial-associated diarrhea; although the significance of this contamination is not clear, it might be a mechanism by which nosocomial spread of infection could occur.

Finally, preliminary data regarding a second toxin ("enterotoxin") of *C difficile* have been published.[90] Although this "new" toxin may eventually be shown to be important in the pathogenesis of disease, the cytotoxin (as indicated above) remains the best marker at this time for *C difficile*-induced diarrhea.

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NIH Consensus Development Conference on CEA (Carcino-Embryonic Antigen): Its Role as a Marker in the Management of Cancer

Sponsored by the

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To Discuss:

- Can CEA be used in screening for cancer?
- Is CEA helpful in the diagnosis of cancer?
- What does CEA tell us about the extent and outcome of cancer?
- Does CEA help in the management and treatment of cancer?
- Can the CEA assay be improved?
- Can CEA be used in combination with other markers?

When: September 29, 30, October 1, 1980

Where: Masur Auditorium
Clinical Center (Building 10)
National Institutes of Health
Bethesda, Maryland

For technical information please contact:
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Suite 220
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Preregistration will be requested

Specialty Conference

Moderator
STANLEY S. FRANKLIN, MD

Discussants
MARSHALL T. HUNT, LLB
THOMAS VOGT, MD
STANLEY S. FRANKLIN, MD
GREGORY WALSH, MD
DONALD E. PAGLIA, MD

An edited transcription of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles, California.

Refer to: Franklin SS, Hunt MT, Vogt T, et al: Hypertension and cerebral hemorrhage: A malpractice controversy—Efficacy of drug therapy, epidemiology, neurological aspects and pathology—Interdepartmental Conference, UCLA School of Medicine (Specialty Conference). West J Med 133:124-140, Aug 1980

Hypertension and Cerebral Hemorrhage: A Malpractice Controversy

Efficacy of Drug Therapy, Epidemiology, Neurological Aspects and Pathology

The plaintiff alleged that failure of the attending physician to manage her husband's hypertension properly resulted in his death from intracerebral hemorrhage. Four lines of evidence supported the defendant: (1) In 1970 to 1971 there was uncertainty in the medical community whether mild hypertension should be treated with drugs; this uncertainty still existed at the time of the trial. (2) Severe hypertension and advanced age are the two most important predisposing factors leading to intracerebral hemorrhage; the deceased patient had neither. (3) Hemorrhage into the cerebral cortex and underlying white matter is not typical of hypertensive intracerebral bleeding; more likely, rupture of an arteriovenous malformation occurred. (4) A diagnosis of hypertensive intracerebral hemorrhage is not one of exclusion but requires objective evidence of vascular change in the brain, heart and kidney; these changes were not found in the deceased patient. In conclusion, an expert witness should testify objectively rather than be the advocate of a lawyer's theory of liability.

STANLEY S. FRANKLIN, MD:* *In this conference we present a* medical-legal *clinicopathologic exercise in which the final judgment was made by a jury of 12 lay persons rather than by a pathologist. This malpractice trial took place in 1977. Mr. Marshall Hunt was defense attorney and Dr. Thomas Vogt was adviser; the discussants, Drs. Franklin, Walsh and Paglia, testified as expert witnesses for the defense.*

The Case for the Plaintiff

MARSHALL T. HUNT, LLB:† A court action for malpractice and failure to treat and control hypertension properly was filed by the widow and 4-year-old child of a deceased patient. It was

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†President, National American Board of Trial Advocates.

alleged that the failure of the attending physician to treat the patient properly resulted in cerebral hemorrhage and death. The patient, a 48-year-old nuclear physicist, had been the president of his own corporation dealing in space technology.

The aim of the plaintiff's medical case was to show that the average blood pressure readings of the patient had been 124/83 mm of mercury from 1959 to 1967, and 154/94 mm of mercury from September 1969 to February 1970 (Table 1). Further, his mother had died of cerebral hemorrhage at age 38, and the patient's electrocardiograms (EKG's) had shown a 30 degree left axis deviation and nonspecific T wave abnormalities. The plaintiff's attorney used his medical witnesses to capitalize on the autopsy findings, which showed a 1.6-cm thick left ventricular wall coupled with the long-standing alleged left axis shift, to establish left ventricular hypertrophy as a result of long-standing hypertension. The experts testified that the statement in the autopsy report—"thin [renal] capsule strips with difficulty from the granular surface"—was indicative of the effects of hypertensive disease. The autopsy report also included descriptions of hyalinized glomeruli and mild medial thickening of arteries.

The plaintiff's medical witnesses (which included two cardiologists, a nephrologist and a forensic pathologist) concluded that there was evidence of long-standing hypertension and hypertensive heart disease with left ventricular hypertrophy, along with hypertensive nephrosclerosis. They capitalized on the fact that the attending physician had received a letter from physicians employed by the patient's life insurance company, advising that on October 14, 1968, the patient's blood pressure reading had been 180/106 mm of mercury.

In February 1970 a regimen of Regroton (50 mg of chlorthalidone and 0.25 mg of reserpine) was prescribed for the patient by the attending physician, a general internist; in March 1970, this dosage was reduced to half a tablet daily. No additional prescription for Regroton was written after the initial one for 100 tablets. During therapy, the average blood pressure reading was 139/85 mm of mercury; on December 19, 1970, the date of the patient's last office visit, it was 140/86.

The patient's wife stated that he had *not* been receiving Regroton from April to November 1970; about a month before his last office visit in November 1970, Regroton therapy was started again. She also testified that on Sunday, March 7, 1971 (four days before his fatal cerebral hemorrhage) her husband was sweating profusely, had dizziness, was pale and complained of headaches. He spent most of the day in bed; however, on the following day he had recovered sufficiently to go to work.

TABLE 1.—*Blood Pressure Recordings of Deceased Patient From 1959 to 1971*

Itinerary of Readings	*Date*	*Blood Pressure Recordings (mm of mercury)*
Prehypertensive values	2-59	120/80
	8-59	120/82
	3-61	128/84
	4-62	124/80
	7-64	122/84
	4-65	134/86
	5-65	110/84
	5-67	134/86
First insurance examination	9-12-69	144/94
	10-14-69	180/106
	11-05-69	146/94
Pretherapy values	1-29-70	138/84
	2-23-70	160/90
Regroton* therapy	3-05-70	138/84
	3-19-70	140/86
	4-15-70	140/86
Last office visit	12-19-70	140/86
Second insurance examination	1-06-71	138/86
	2-26-71	140/86
Postcerebral hemorrhage	3-11-71	210/110

*50 mg chlorthalidone, 0.25 mg reserpine.

On Thursday, March 11, he spent the morning at an aerospace meeting and came back to his office in the afternoon. He was talking to his wife on the telephone when he suddenly stopped. His secretary came into the room, found him immobile, and rushed him to the University of California, Los Angeles, (UCLA) Hospital. On arrival, an examination showed an obtunded, aphasic patient with a right-sided hemiparesis and a blood pressure that measured 210/110 mm of mercury. Soon thereafter, he lapsed into a coma and showed decerebrate posturing and fixed dilated pupils. In spite of steroid and mannitol therapy, he later showed an absent oculo-vestibular response to cold water testing, cessation of spontaneous respiration and electrocerebral silence on electroencephalography. He died on Saturday, March 13—48 hours after admission; a postmortem examination confirmed massive intracerebral hemorrhage as the primary cause of death.

The aim of the plaintiff's medical case was that the paramedical history and autopsy report showed long-standing hypertensive disease; the

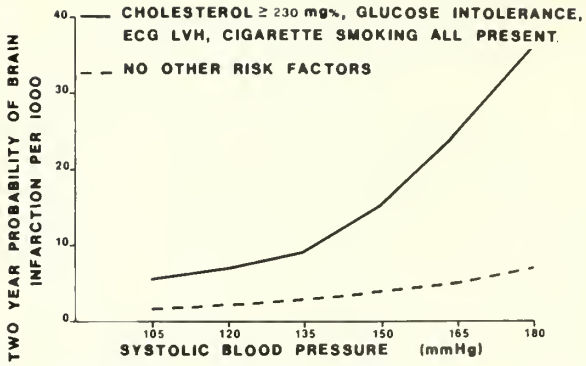

Figure 1.—Two-year probability of atherothrombotic brain infarction per 1,000 according to level of systolic blood pressure (mm of mercury) and the presence or absence of other risk factors in the Framingham Study. (Adapted from several sources.)

failure of the attending physician to monitor the patient after April 1970 and allowing Regroton therapy to be discontinued had resulted in his stroke on March 11, 1971. The deceased had been a patient of this attending physician since 1959, and his previous history had been of gastric distress. The plaintiff's cardiologist testified that because of both the patient's own medical history and that of his mother, it should have been mandatory that the patient receive hypertensive drugs; he should have been continuously monitored and supervised as well. He further testified that the standard procedure in 1970 was that a 48-year-old patient with a blood pressure of 130/90 mm of mercury would have been treated with antihypertensive drugs.

In addition, the plaintiff's attorney argued that the general practitioner must be held to the same care and skill ordinarily used by reputable specialists and that it was no defense that he did "the best he could." The plaintiff denied existence of alternate methods of diagnosis or treatment and argued that it was mandatory that the patient should have received antihypertensive therapy; the failure to continue that therapy violated standard practice and was a proximate cause of the patient's death.

The Defense

The aim of the defense through medical witnesses was to establish that there was more than one recognized method of diagnosis and treatment during 1969 to 1971. It was further argued that the autopsy report was not indicative or conclusive of hypertensive disease; that the "trial" of Regroton did not result in any dramatic change of blood pressure; and that the physician, by discontinuing Regroton therapy, followed a practice consistent with one of the approved standard practices in the community at that time. Subsequent information obtained from insurance underwriters disclosed that the deceased had applied for additional life insurance in January 1971. Blood pressure readings of 138/86 mm of mercury were recorded on January 6, 1971, and of 140/86 mm of mercury on February 26, 1971, the last reading just 13 days before his fatal cerebral hemorrhage.

The jury was further advised that the evidence shows that the blood pressure of the patient on admittance to the UCLA Hospital was the proximate result of the cerebral vascular accident (CVA) and was not indicative of his blood pressure at or about the time preceding the CVA. The jury was also advised that the medical evidence shows that the use of Regroton would not have prevented the CVA. During the last two weeks before his death, the patient had undergone severe emotional stresses; he had been unable to obtain financing for his business and he was irreversibly on the brink of bankruptcy.

Initiating Antihypertensive Therapy

THOMAS M. VOGT, MD, MPH:* For more than 20 years it has been recognized that there is a consistent association between the level of blood pressure and the likelihood of subsequent cardiovascular disease. However, association and cause are not necessarily equivalent terms; this is clearly shown by examining the record of recommendations for treating elevated blood pressure during that time. In the late 1950's several investigators[1-5] showed the benefits of antihypertensive therapy in the treatment of malignant hypertension. During those years drug therapy was limited to persons with extreme levels of blood pressure even though the associations between blood pressure and morbidity and mortality seemed to be continuous functions. An understanding of when to initiate therapy is crucial to the control of morbidity resulting from hypertension because most patients with hypertension fall into the category of mildly elevated blood pressure (90 to 104 mm of mercury, diastolic pressure).

Figure 1 (from the Framingham study) shows the risk of brain infarction according to systolic blood pressure and the presence or absence of

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other risk factors. The rise in risk is evident even within blood pressure levels considered normal, and this rise is dramatically accentuated when other factors are present.

The findings from the Framingham study gave rise to so many data that tables were calculated[6] using the major risk factors of blood pressure—smoking and serum cholesterol levels—to calculate the probability of an event during a given time (Table 2). Table 2 shows that in a 65-year-old man without glucose intolerance, who smokes and whose serum cholesterol level is 285 mg, there is a 1.2 percent probability of a thrombotic stroke occurring in eight years if his systolic blood pressure is 120 mm of mercury, and a 4.2 percent chance if his systolic pressure is 165 mm of mercury. Obviously, these are hypothetical figures, but they do reflect estimates that are very accurate for populations, if not individual persons. The difficulty was that no one could be certain that using drugs to lower blood pressure would necessarily result in an equivalent reduction in statistical risk. Because all antihypertensive drugs have side effects when used frequently, and because they are expensive when used as life-long therapy, there was considerable reluctance to translate statistical information into therapeutic practice.

In 1971 Paul[7] summarized the data relating blood pressure to subsequent cardiovascular disease in six major prospective studies. These studies uniformly indicated that diastolic blood pressure of 85 to 104 mm of mercury, as recorded on an initial visit, had unfavorable effects on the total death rate, deaths from coronary disease, major coronary events and cerebrovascular episodes. However, these data were statistical, and not experimental in nature.

To resolve the dilemma, several studies were done to test the effects of treatment of nonmalignant forms of hypertension on disease outcomes. Unfortunately, most of the early attempts were marred by inadequate control subjects,[8,9] or were of limited importance because of few patients or short follow-up periods, or both.[10,11] The Veterans Administration Cooperative Study on Antihypertensive Agents[12] was an attempt to examine the effects of therapy on many persons with hypertension in a randomized, prospective format. Enrolled participants had to pass strict requirements for sustained elevations in blood pressure as well as to show strong evidence for compliance with recommended regimens. Random assignment of patients to groups in the study began in April 1964. In May 1967 the study was prematurely terminated for the subgroup of 143 persons, whose diastolic blood pressures averaged 115 through 129 mm of mercury at the time of assignment, because of the high prevalence of morbid events in the placebo-treated group as compared with the drug-treated group.[12] The 380 persons whose blood pressures at the time of random assignment were between 90 and 114 mm

TABLE 2.—*Probability (per 1,000) That in a 65-Year-Old Man Who Smokes Cigarettes Atherothrombotic Brain Infarction Will Develop During the Next Eight Years According to Specified Characteristics (Framingham Study)**

Cholesterol (mg per dl)	*Systolic Blood Pressure (mm of mercury)*						
	105	120	135	150	165	180	195
185	8	13	19	29	44	66	98
210	8	13	19	29	44	65	96
235	8	12	19	29	43	64	95
260	8	12	19	28	42	63	94
285	8	12	18	28	42	62	92
310	8	12	18	27	41	61	91
335	8	12	18	27	40	61	90

*Data from McGee.[6]

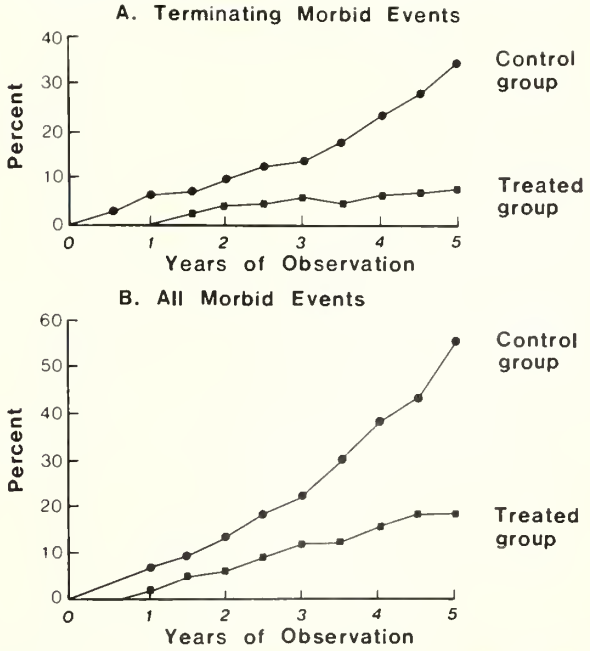

Figure 2.—Veterans Administration Cooperative Study on Antihypertensive Agents: estimated cumulative incidence of morbidity over five years as calculated by life table method; terminating morbid events **(upper graph)** and all morbid events **(lower graph)**; mean with average diastolic blood pressures 90 to 114 mm of mercury at entry. (Reproduced by permission of author and publisher from VA Cooperative Study Group on Antihypertensive Agents,[13] Copyright 1970, American Medical Association.)

of mercury were continued in the program until 1969. The results of that section of the Veterans Administration study are shown in Figure 2.[13] Deaths and significant morbid events were reduced in the treated group, and this reduction was significant only for patients with cerebrovascular events and for patients with congestive heart failure. This information, published in 1970, might have settled the controversy for some, but for others, disturbing gaps in knowledge remained. Statistically, there are substantial differences in risk between persons with diastolic pressure levels of 105 to 114 mm of mercury and those with levels of 90 to 104 mm of mercury. Did the Veterans Administration evidence constitute grounds for treating everyone with mild hypertension?

A survey of recommendations for treatment from that period shows the confusion. In a series of symposia by Walcott and associates,[14] entitled "Therapeutic Dilemmas," the following was stated: "I think it is the practice of most of us to begin treatment in cases with a borderline pressure, say something of the nature of 150 systolic with 90 to 110 diastolic." This was published in October 1970, about three months after publication of part II of the Veterans Administration study.

To decide when to initiate therapy, Thurm[15] in 1970 recommended estimating the severity of hypertension by combining the measured blood pressure with cerebrovascular, ophthalmologic, renal and cardiac findings on a point scale. He recognized that benefits of therapy in patients with mild hypertension were not known and felt that these other findings could help to make the clinical decision.

Also in 1970, Dollery,[16] an English pharma-

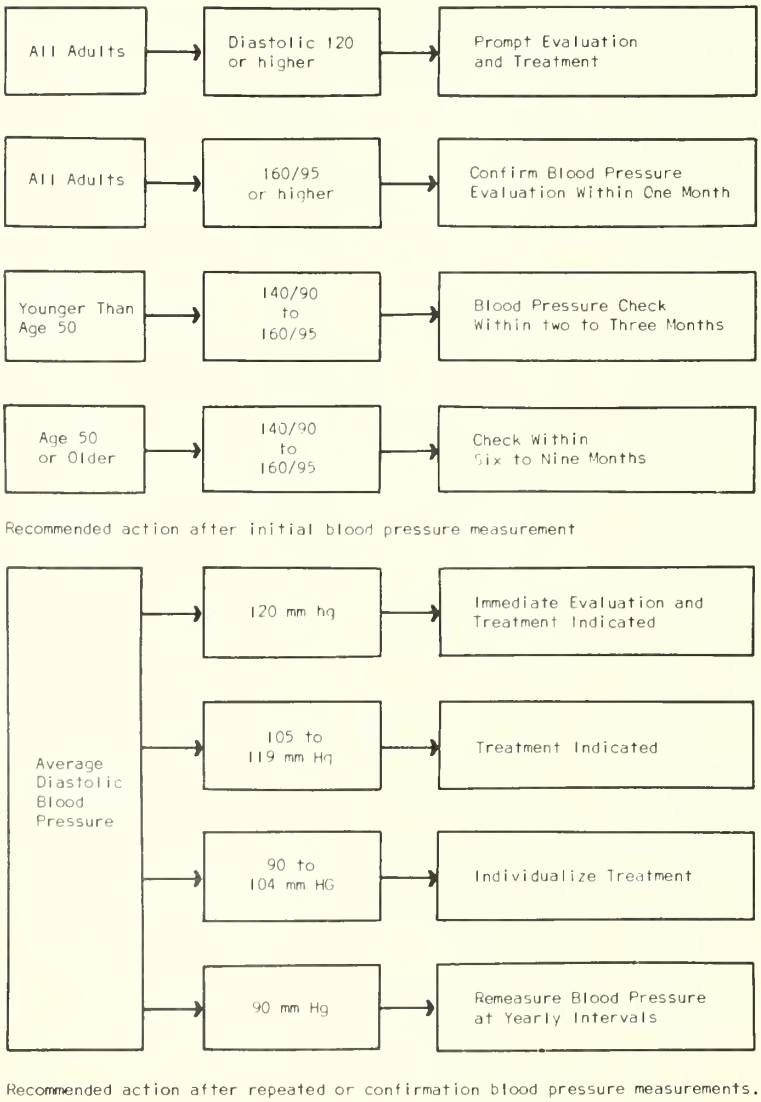

Figure 3.—Recommendations by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure for action on initial and confirmed blood pressure measurements. (Reproduced by permission of author and publisher from Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure,[18] Copyright 1977, American Medical Association.)

cologist, carried this concept of multiple risk a step further. He wrote:

It is important to recognize that the physician who is assessing a patient with mild hypertension must attempt to assess the risk. For example, it would be illogical to start treatment to lower a mildly elevated blood pressure and neglect the fact that the patient smoked heavily. In practice the interpretation of these factors means that the physician is readier to treat when the pressure is higher than when it is lower, more concerned if the patient is young and a man than if she is old and a woman. It is no longer sensible to ask a question such as, "I have a patient with a blood pressure of 170/105 mm Hg, should I treat him?" The answer depends upon an account of all the important factors that play upon risk.

If some physicians were hedging at this time, others were not. Seedat,[17] also in 1970, stated unequivocally, "I regard patients as having established hypertension only when they have a diastolic blood pressure of 110 mm Hg or more, with definite fundal, cardiac and/or renal changes." No one was willing to oppose this, by stating that everyone with a diastolic blood pressure over 90 mm of mercury should be treated.

Even today such certainty is difficult to come by. Figure 3 is taken from the Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[18] Issued in January 1977, this document is the report of a task force of the National High Blood Pressure Education Program of the National Heart, Lung and Blood Institute; its aim was to produce practical recommendations for identifying the segment of the population with high blood pressure, and determining who might benefit from treatment and what therapeutic regimens should be used. For patients with diastolic blood pressure within the range of 90 to 104 mm of mercury, the recommendation was to "individualize treatment." These recommendations were made because further analysis of the Veterans Administration study showed that patients receiving active therapy had good blood pressure control and had a lower frequency of cardiovascular events than patients with less effective control; the latter had fewer events than the placebo group.[19] The Hypertension Cooperative Study Group failed to show that antihypertensive therapy led to decreased likelihood of recurrence of stroke in stroke survivors.[20]

In May 1977 the results of a ten-year intervention trial conducted on patients with mild hypertension by the US Public Health Service were published.[21] The results were not clear-cut:

In subjects with mild hypertension, no discernible target organ damage, and no other predisposing disorders, whose pressures were well controlled with antihypertensive agents for a period averaging seven years, there was no reduction in death or coronary heart disease when compared to placebo controls. Active drug treatment was over 50 percent effective in preventing other lesser complications such as electrocardiographic evidence of left ventricular hypertrophy and radiographic cardiac enlargement.

In the trial, acceleration of hypertension was limited to the placebo-treated group in which 12.2 percent of the cases were treatment failures that necessitated active therapy.

All of this does not suggest that there is no benefit from the treatment of mild hypertension. The size and duration of the trials done recently have been inadequate to show apparent clinical improvement reflected in decreased mortality, because the effects are less dramatic than they are for higher levels of blood pressure. Failure to show a significant difference in mortality during seven years in this group suggests to many, including the authors of the US Public Health Service study, that there is no urgency in initiating drug therapy, and that "systematic follow-up without drugs while attempting hygienic intervention and control of other risk factors may be a reasonable alternative for this large group."[21]

Perhaps the most relevant statement from the literature for the case under discussion is one taken from a paper written by Freis[22] in 1972:

What, then, does the clinician do when he is faced with a new patient who has a diastolic blood pressure in the range 90 to 110 mm Hg, no evidence of vascular damage in the fundi, no cardiac symptoms, no evidence of left ventricular enlargement on the electrocardiogram or roentgenogram and normal renal function? First he should inquire into the family history. Did the mother, father or siblings have hypertension; if any have died what was the fatal event and at what age did death occur? A history of relatively early death due to a complication of hypertension in either or both parents is a good indication for treatment. The chances are great that hypertensive cardiovascular disease also will develop if the patient is not treated.

In summary, there is an increasing appreciation of the importance of diastolic blood pressure readings that exceed 90 mm of mercury, and also of the need to place them in the context of the patient's other risk factors. It is equally clear that the diastolic pressure is not more important than systolic pressure in estimating risk, and mean blood pressure may be the best estimate of all. However, it is still not possible to gain a uniform consensus on whether persons who lack hypertensive complications should be medically treated if their diastolic blood pressure falls between 90 and 104 mm

of mercury. Alternative therapies such as weight loss, salt restriction and medication may, in selected cases, be successful in controlling such elevations. (The findings of the Hypertension Detection and Follow-up Program[23] indicate a significant reduction in mortality among persons with diastolic blood pressure ranging from 90 to 104 mm of mercury who were treated with drugs when compared with referred control subjects. Thus, this controversy may soon be resolved.)

The patient under discussion did have a history of left axis deviation of the heart that was stable for more than 12 years. But because the patient had well-documented normotension for the first of these 12 years, left axis deviation cannot be ascribed to hypertensive heart disease. His mother did die of a cerebral hemorrhage of unknown cause at a young age. Whether this constitutes sufficient information for Freis[22] in 1970 to have begun therapy in a patient with average blood pressure readings of 154/94 mm of mercury is not clear. On the other hand, with the controversy that existed in the medical literature in 1970, the physician in this case used therapy that fell within one of several accepted standard practices existing in the community for the treatment of mild hypertension.

Epidemiology and Pathophysiology of Hypertensive Cerebral Hemorrhage

Dr. Franklin: Intracerebral hemorrhage is a unique pathological phenomenon and one of the most dramatic clinical states in medicine; yet its pathophysiology is not appreciated by most physicians. Demographic factors of cardinal importance in the development of cerebral hemorrhage are race, presence of systemic hypertension and advanced age. Asians and blacks have a higher prevalence of cerebral hemorrhage than do whites.

Hypertension has been incriminated as a positive factor in 80 percent to 90 percent of patients with cerebral hemorrhage. Stehbens[24] showed left ventricular hypertrophy in 87 percent of 347 patients with cerebral hemorrhage as reflected in increased heart weight of greater than 400 grams in women, and greater than 420 grams in men, thus supporting the old aphorism, "The large heart breaks the weak vessels." Fukuda[25] in Japan showed a close correlation between elevated arterial blood pressure of more than 170 mm of mercury systolic and 110 mm of mercury diastolic, and the frequency of cerebral hemorrhage.

Advanced age may be an important predisposing factor in cerebral thrombosis, as evidenced from the data in the Framingham Study.[26] Elevated systolic blood pressure has little or no effect on the prevalence of cerebral thrombosis in persons below the age of 45 years, and does not exert a major effect until after the age of 60. In contrast to cerebral thrombosis, there is insufficient epidemiologic data reflecting age and extent of hypertension in patients with cerebral hemorrhage. Clinical experience, however, suggests that cerebral hemorrhage is not uncommon in young and middle-aged adults, as well as being frequent in older patients.

Bearing on the importance of hypertension as a causal factor in strokes is the extent of variation in blood pressure in so-called normotensive persons. Bevan, Honour and Scott,[27] using a portable automatic apparatus to measure intra-arterial pressure, recorded values continuously for more than 24 hours. They found considerable variation in blood pressure measurements in normotensive and hypertensive subjects, with the highest readings more than twice the lowest values found in many normal persons.

Similarly, Masters and Johnson[28] found that during coitus systolic blood pressure in men increases from 40 to 100 mm of mercury and diastolic blood pressure from 20 to 50 mm of mercury.

With blood pressure during stress frequently reaching 220/130 mm of mercury in normal subjects, what protects humans from cerebral artery blowouts? This protection is best explained by the physiological mechanism for regulation of cerebral blood flow[29] (Figure 4). When systemic blood pressure rises or falls, the cerebral arteries constrict or dilate, respectively, to insure a constant cerebral blood flow. This phenomenon, termed autoregulation, occurs in the small resistant cerebral arteries and is probably myogenic in origin, rather than depending on a neurogenic mechanism. As shown by Strandgaard and colleagues,[29] when mean blood pressure exceeds a critical level of 150 to 200 mm of mercury, a breakthrough of autoregulation with an increase in cerebral blood flow occurs, leading to damaged blood vessels and extravasation of fibrin, erythrocytes and edema.

How may the stress of chronic hypertension of a degree less than the breakthrough level affect cerebral blood vessels? Ross-Russell[30] has suggested that long-standing hypertension produces a breakdown in vascular resistance, leading to mechanical distention, impaired vessel wall integ-

rity, dilation and, eventually, rupture with hemorrhage.

Evidence during the past 15 years has incriminated microaneurysms in the small penetrating arteries (of less than 1 mm in diameter) as playing a major role in the breakdown of vascular resistance of most hypertensive cerebral hemorrhages that occur in persons older than 45 to 50 years of age. Originally described by Charcot and Bouchard[31] in 1868, microaneurysms have been linked with cerebral hemorrhage by the work of Ross-Russell in 1963.[32] Using a method of postmortem angiography, he showed that microaneurysms were found in many patients who had died of cerebral hemorrhage. Cole and Yates[33] extended Ross-Russell's observations. Using a similar postmortem method of examination, they studied the brains of 100 hypertensive and 100 normotensive patients who were matched for age and sex. The results were as follows: (1) Of 53 brains with evidence of microaneurysms, 46 were in hypertensive patients who were, in all but two cases, at least 50 years old. (2) Only 7 of the 100 brains of normotensive patients showed a few microaneurysms and all were in patients 66 years or older. (3) In 18 of the 20 patients with cerebral hemorrhage (average age 61 years), multiple microaneurysms were detected. (4) A 34-year-old black man who had died of malignant hypertension and cerebral hemorrhage showed fibrinoid necrosis of cerebral blood vessels but no microaneurysms. (5) Cerebral hemorrhage and microaneurysms occurred in the same location, that is, basal ganglia and subcortical regions supplied by penetrating small arteries off the main cerebral vessels; these microaneurysms frequently showed evidence of minor hemorrhage.

Therefore, as summarized by Pickering in 1974,[34]

> The disease causing cerebral hemorrhage is quite different from that causing cerebral thrombosis and myocardial infarction. The former is the disease of small cerebral arteries in which the media gives way causing aneurysm and rupture. The latter is a disease of large arteries all over the body in which intimal plaques narrow the lumen which is ultimately closed by thrombus. Only two factors are yet known in the pathogenesis of Charcot-Bouchard aneurysms: age and arterial pressure.

In preparation for this trial, additional epidemiologic data were obtained from three sources: vital statistics from death reports,[35] and the Veterans Administration and US Public Health Cooperative studies[13,21] on the treatment of hypertension.

Vital statistics from death reports prepared by physicians are inaccurate, when compared with autopsy findings. Heasman and Lipworth[36,37] noted that cerebral hemorrhage was incorrectly certified in 43 percent of cases during the 1960's, the era preceding the use of computerized axial tomographic (CAT) scanning. Therefore, only gross trends can be determined from vital statistics

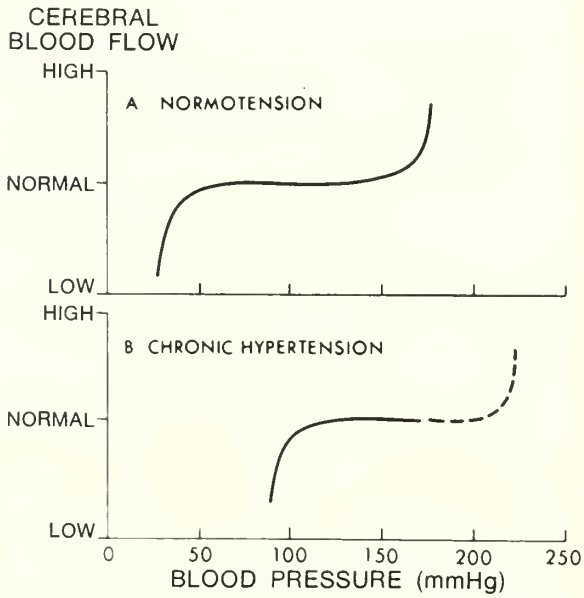

Figure 4.—The relationship between cerebral blood flow and mean blood pressure in **(A)** normotensive persons and in **(B)** chronic hypertensive subjects, with the broken lines indicating breakthrough of autoregulation after further elevation of blood pressure with pressor agents.

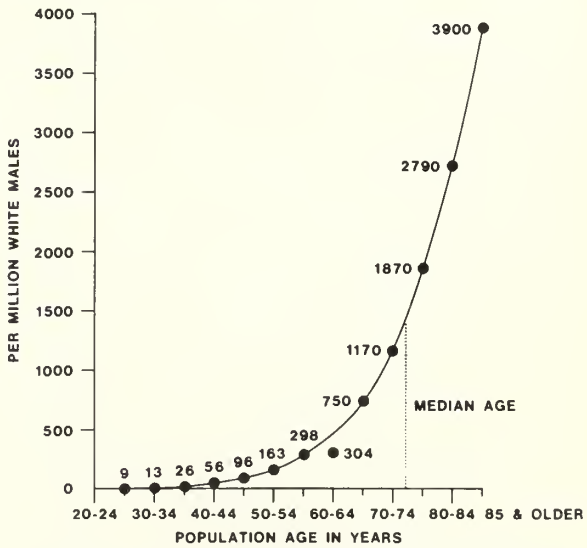

Figure 5.—Relationship of age to occurrence of deaths from cerebral hemorrhage in white men in the United States (1970).

data. In 1970 occurrence of death in the United States from cerebral hemorrhage in white men was closely correlated with advancing age; the median age of death from cerebral hemorrhage was 72 years (Figure 5). The chance that this 48-year-old man would die of cerebral hemorrhage was 1 in 10,000; the chance that his mother would die of cerebral hemorrhage at age 38 was 1 in 43,000. In contrast, chances of dying of cerebral hemorrhage were 12 times greater at age 70 and 41 times greater at age 85, as compared with dying at age 48.

In the Veterans Administration Cooperative Study,[13] 25 of 194 placebo-treated middle-aged male patients had strokes: 20 had cerebral thromboses and 5 hemorrhagic strokes (3 intracerebral hemorrhages and 2 cases of subarachnoid bleeding) (Table 3). The mean age of death was 62 years for those dying from thromboses, and 49 years for those dying from hemorrhagic strokes. There were almost twice as many blacks as whites in the hemorrhagic stroke group compared with those with cerebral thrombosis. Duration of the placebo treatment before the onset of stroke was about three years per patient in each group. Prerandomized mean blood pressure readings were comparable in both groups, although patients sustaining cerebral thromboses showed a somewhat higher systolic blood pressure, reflecting a 13-year seniority in age over those patients with hemorrhagic stroke. Data of blood pressure readings recorded at the patients' last clinic visits before their strokes were obtained from stored computer tapes provided by Dr. Edward Freis, Chairman of the Veterans Administration Cooperative Study. The prestroke blood pressure values were not significantly different from the prerandomized values in the 20 patients with cerebral thromboses, but

TABLE 3.—*Occurrence of Strokes in 25 Placebo-Treated Patients With Diastolic Blood Pressure Levels of 90 to 114 mm of Mercury**

	Strokes	
	Cerebral Thromboses	*Hemorrhage*
Number of patients	20	5†
Percentage of patients	10%	3%
Mean age (years)	61.7	48.6
Percentage of white patients (expected/actual)	58%/62%	58%/33%
Duration of follow-up before stroke (years)	2.9	3.4
Prerandomized BP (mm of mercury)	174/102 } NS	158/107 } P<.001
Prestroke BP (mm of mercury)	173/106 } NS	190/127 } P<.001
Change in BP (mm of mercury)	−1/+4	+32/+20

BP = blood pressure; NS = not significant

*Veterans Administration Cooperative Study.
†Three intracerebral hemorrhages and two cases of subarachnoid bleeding.

TABLE 4.—*Rarity of Cerebral Hemorrhage in Middle-Aged Patients With Mild to Moderate Hypertension*

	VA Cooperative Study	*USPH Cooperative Study*	*Total*
Number of control patients	194	196	390
Mean age (years)	52.0	44.0	48.0
Mean follow-up (years)	2.9	5.7	4.3
Follow-up in patient-years	542	1,124	1,676
Mean clinic BP (mm of mercury)	165/105	148/99	157/102
Morbid events	51	27	78
Cerebral thrombosis	20	6	26
Cerebral hemorrhage	0	0	0

BP = blood pressure; USPH = United States Public Health; VA = Veterans Administration

TABLE 5.—*Interaction of Hypertension and Age of Patients in the Production of Cerebral Hemorrhage*

Diastolic Blood Pressure (mm of mercury)		
130+	*129-105*	*104-90*
Rapid development	Gradual development	Gradual development
Fibrinoid necrosis (any age)	Many microaneurysms (45 years and older)	Fewer microaneurysms (60 years and older)

increased notably in all five patients with hemorrhagic strokes. There was a mean increase of 32 mm of mercury systolic and 20 mm of mercury diastolic pressure, reaching an average blood pressure of 190 systolic over 127 diastolic in the severe hypertensive range. According to the protocol requirements, four patients barely missed starting antihypertensive therapy before a hemorrhagic stroke occurred, and the fifth patient had a stroke after beginning drug treatment.

Further data on mild to moderate hypertension in middle-aged patients were obtained from the report of the United States Public Health Cooperative Study Group published in 1977.[21] Table 4 shows a comparison of the results of the investigations done by the Veterans Administration Cooperative Study Group and the United States Public Health Cooperative Study Group. The latter group of patients were younger, included fewer black patients, had lower blood pressure and sustained a lower rate of blood pressure acceleration, thereby suggesting, overall, a less severe incidence of hypertension. The incidence of strokes in both series was generally low, befitting a middle-aged population, with 26 cerebral thromboses (without any mortality) in 1,675 patient-years of placebo-treated hypertension, or one cerebral thrombosis per 645 patient-years. In contrast, there were no documented hemorrhagic strokes in 390 patients with 1,676 patient-years of placebo-treated mild and moderate hypertension. This population averaged 48 years of age, had an average blood pressure of 157/102 and had a follow-up period that averaged 4.3 years per patient. Conclusions from these studies strongly supported Pickering's[34] thesis that severity of hypertension and advanced age are the most important predisposing factors in cerebral hemorrhage (Table 5).

With malignant hypertension of short duration (weeks or months), cerebral hemorrhage can occur at any age, and it is secondary to fibrinoid necrosis of vessel walls rather than formation of microaneurysms. With severe hypertension present for years, microaneurysms develop in middle-aged subjects and can ultimately rupture, producing cerebral hemorrhage. In contrast, in geriatric patients microaneurysms and, ultimately, cerebral hemorrhages may develop with only mild to moderate hypertension of long duration.

The patient in this trial, a 48-year-old man, and his 38-year-old mother both died of cerebral hemorrhage; these represent two rare paired events that are highly unlikely to occur by chance alone. Thus, these two deaths occurred most likely as a result of inborn defects of cerebral blood vessels, such as arteriovenous malformations or small angiomas, rather than as a result of mild hypertension of short duration.

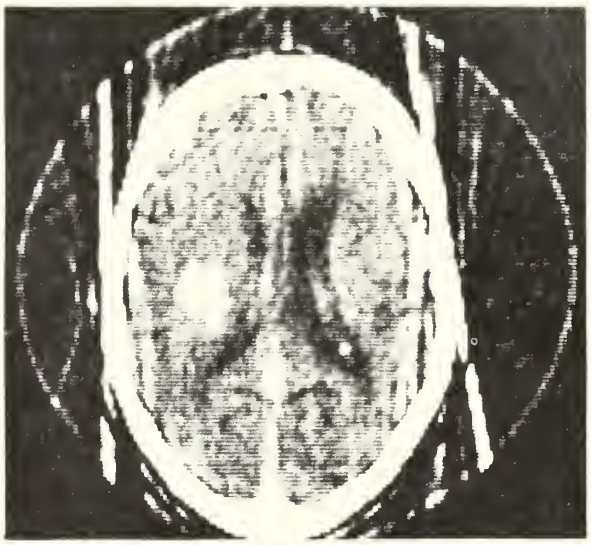

Figure 6.—Computerized axial tomogram of intracerebral hemorrhage.

Neurological Aspects of Intracerebral Hemorrhage

GREGORY O. WALSH, MD:* Because of the difficulty in diagnosing intracerebral hemorrhage correctly before the advent of computerized axial tomography (CAT), several misconceptions have arisen about the clinical presentation of patients with this disease entity: the onset is sudden and catastrophic, headache is always present, impaired consciousness or coma invariably ensues, spinal fluid is always bloody, mortality is high and intraventricular hemorrhage always fatal, and hypertension is invariably present and severe.

The above clinical features, as described in the earlier literature,[38] are most characteristic of patients with large hematomas that develop rapidly and produce a mass effect on brain function. Improved diagnosis with computerized axial tomographic scanning of the brain has made it easier to identify a smaller lesion or a slowly developing large intracerebral hemorrhage without mass effect. Before CAT scanning, these latter lesions (from which patients frequently recovered) would have been misdiagnosed as cerebral thrombosis

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or embolism. Therefore, the clinical entity of intracerebral hemorrhage needs to be redefined.

Computerized axial tomographic scanning shows intracerebral hemorrhage as a dense homogeneous white zone with clear borders surrounded by darker areas of the brain and cerebral spinal fluid (Figure 6). Using this method, together with a careful history and neurological examinations, Caplan and Mohr[39] reported their findings on 60 patients with intracerebral hemorrhage in the Harvard Stroke Study. In 72 percent of patients, the onset of the hemorrhage was gradual, taking minutes, hours or days to develop; in only 25 percent of patients was the deficit maximal when the patient was first examined. No patient with a hemorrhage had a stepwise, stuttering or fluctuating course of illness.

In the Harvard Stroke Study of patients with intracerebral hemorrhage, headaches developed in 28 percent of patients when symptoms occurred; in 12 percent they occurred later, and in 40 percent, headaches never developed at all. The other 20 percent of patients were in a coma and, therefore, no history of headache could be obtained. When initially seen, 50 percent of the patients were alert, 23 percent lethargic and 27 percent in coma. Mortality was 50 percent; however, in 20 percent of the patients who survived, only slight deficits remained on discharge.

TABLE 6.—*Differential Diagnosis of Intracerebral Hemorrhage*

Diagnoses
Hypertension
Blood vessel anomalies—aneurysm or arteriovenous malformation
Anticoagulation
Collagen vascular disease
Brain tumor—metastatic or primary
Hemorrhagic infarction
Blood dyscrasia (such as leukemia or thrombocytopenic idiopathic purpura)
Trauma
Idiopathic

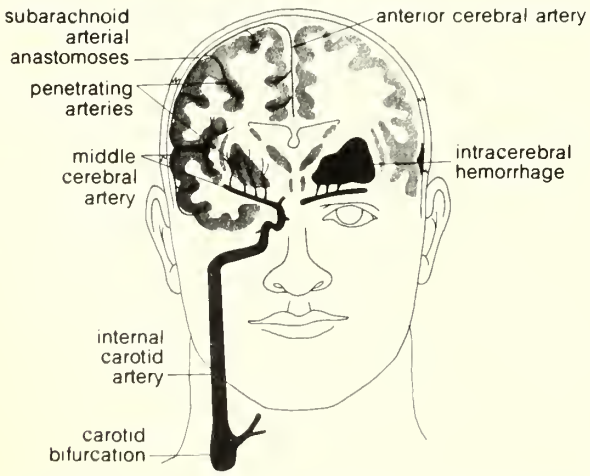

Figure 7.—Drawing of penetrating vessels and intracerebral hemorrhage. (Reproduced by permission of authors and publisher from Cooper and West.[41])

In the Kinkel and Jacobs[40] series of 21 patients with intracerebral hemorrhage identified by CAT scanning, the clinical diagnosis was incorrect in 9 patients (43 percent). Lumbar puncture showed xanthochromic cerebral spinal fluid in 11 patients (52 percent). Contrary to the view that intraventricular hemorrhage is invariably fatal, three of the five patients with this complication survived.

Hypertension is the most common cause of intracerebral hemorrhage (Table 6). In contrast to the classic type of massive intracranial hemorrhage, which is preceded by hypertension in about 90 percent of the patients in earlier series,[38] 41 percent of patients with hemorrhagic strokes in the Harvard Stroke Registry[39] and 52 percent of patients in the Kinkel and Jacobs[40] series had no antecedent history of elevated blood pressure. Many of these normotensive patients who sustained intracerebral hemorrhage were receiving anticoagulants.

Intracerebral hemorrhage resulting from hypertension usually occurs at the site of penetrating arteries, such as where the lenticulostriate arteries emanate from the large middle cerebral artery.[32,33] These vessels supply the basal ganglion and internal capsule (Figure 7).[41] In the series of patients with hypertensive intracerebral hemorrhage studied by Coles and Yates,[33] 70 percent of hemorrhages occurred in the lenticular striate or putamen, 25 percent in the pons and 5 percent in the cerebellum. In one normotensive patient the hemorrhage occurred in the parietal cortex and white matter. Of the patients with hypertensive hemorrhages studied by Caplan and Mohr,[39] about 50 percent of hemorrhages occurred in the putamen or lateral basal ganglion, 8 percent to 25 percent in the thalamus, 8 percent in the pons and 12 percent in the cerebellum. Hemorrhages also occurred in small blood vessels emanating from larger blood vessels where pressure is higher.

The site of hypertensive intracerebral hemorrhage corresponds to the sites of microaneurysms found at autopsy, using special techniques of microangiography and microdissection.[33] The most common sites of microaneurysms were

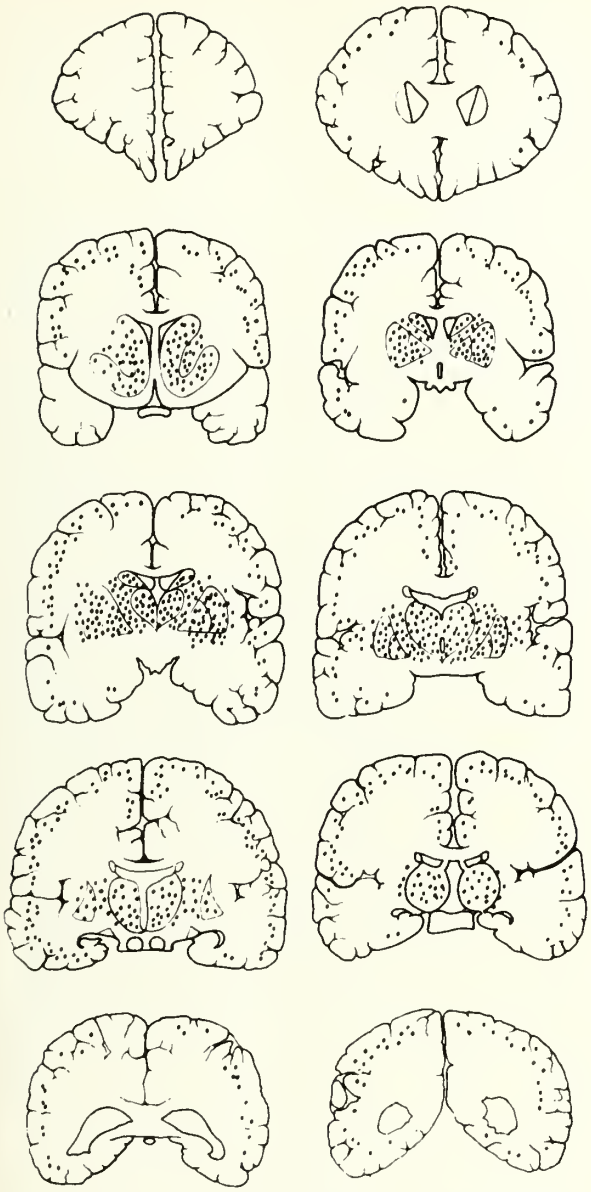

Figure 8.—Sites of all aneurysms discovered in the cerebral hemispheres in 53 patients. Successive front to back sections of brain left to right in successive rows. (Reproduced by permission of authors and publisher from Cole and Yates.[33])

the putamen, globus pallidus, thalamus, and pons (Figure 8). Subcortical white matter also shows the presence of occasional microaneurysms but not hypertensive hemorrhages. In contrast to hypertensive intracerebral hemorrhage, a cortical or white matter hemispheric intracerebral hemorrhage is probably caused by excess anticoagulation therapy, arteriovenous malformation or aneurysms.

The clinical presentation of a patient depends on the area of brain involved (Table 7). Putamen hemorrhages affect the internal capsule, resulting in the patient having contralateral hemiplegia, conjugate gaze paresis to the side of the hemiparesis and normal pupils. In patients with thalamic lesions, symptoms include hemisensory deficits, hemiparesis, conjugate gaze deficit to either side, upward gaze palsy with eyes down and in, sixth nerve pseudopalsy, and small, poorly reactive pupils. In those with pontine lesions, quadraparesis, horizontal gaze paresis, preserved reflex vertical gaze and small reactive pupils often occur. In patients with cerebellar hemorrhages symptoms include vomiting and ataxia, as well as sixth nerve gaze palsy to the side of the hemorrhage, and small or normal size reactive pupils.

Computerized axial tomograms can be helpful in predicting the cause of intracerebral hemorrhage. Hematomas in the sylvian fissures are usually related to middle cerebral artery aneurysms. A cavum septum pellucidum hematoma is almost pathognomonic of an aneurysm of the anterior cerebral complex. Lenticular striate hematomas are probably related to hypertension. Bleeding into the cortex or underlying white matter may be related to arteriovenous malformations or excess anticoagulation therapy. The arteriovenous malformation may be difficult to find, particularly with the destruction of underlying tissue from hemorrhage.

Although this patient's hemorrhage occurred

TABLE 7.—*Clinical Signs in Intracerebral Hemorrhage*

Site	*Motor/Sensory*	*Extraocular Movements*	*Pupils*
Hemisphere	Unilateral paresis (may be absent)	Normal or conjugate gaze paresis to side of hemiparesis	Normal
Putamen	Hemiplegia	Conjugate gaze paresis to side of hemiparesis	Normal
Thalamus	Hemiparesis	Conjugate gaze deficit to either side, upward gaze palsy, skewing, eyes down and in, sixth nerve pseudopalsy	Small, poorly reactive
Pons	Quadriparesis	Horizontal gaze paresis to both sides; preserved reflex vertical gaze	Small, reactive
Cerebellum	Ataxia gait	Sixth nerve or gaze palsy to side of hemorrhage	Small or normal size, reactive

in the left parietal occipital region, and also involved the entire internal capsule communicating with the ventricular system and then extended into the midbrain to the level of the pons, it is impossible to tell the origin of the hemorrhage. It may not be related to hypertension but to a small arteriovenous malformation or angioma that was destroyed at the time of the bleeding. The problem is whether the hemorrhage started in the parietal occipital cortex and then spread deep into the internal capsule or vice versa. If it started in the cortex or underlying white matter, it is unlikely that it resulted directly from the hypertensive disease. If it started in the internal capsule, where large arteries go directly into smaller penetrating arteries, and then spread into the white matter of the parietal occipital lobe, it is more likely to have been due to a recent and pronounced increase in blood pressure that acted on a relatively unprotected capillary bed.

At the time of admission to the UCLA Hospital the patient's blood pressure was 220/110 mg of mercury, which is much higher than the previous recorded pressure of 140/90 mm of mercury. This increased pressure may have been related to the Cushing reflex secondary to increased intracranial pressure from pontine hemorrhage. It is impossible to determine which came first: the blood pressure causing the hemorrhage or the hemorrhage causing increased intracranial pressure and resulting in increased blood pressure secondary to the Cushing reflex.

The Pathology of Hypertension: Kidneys, Heart and Brain

DONALD E. PAGLIA, MD:* It is important to recognize, especially in the medical-legal context, that the clinical entity termed hypertension is not accompanied by distinct pathognomonic lesions. The postmortem diagnosis of hypertension, therefore, becomes an educated conclusion based as much on clinical data collected before death as on identification of certain tissue alterations that typically do accompany the disease. These alterations are primarily vascular, but they include a number of secondary changes in susceptible target organs. Most prominently affected are the kidneys, heart and brain, and this discussion will be limited to those organs, while recognizing that any tissue may be affected to some degree by what is essentially a diffuse, albeit variable, vascular impairment.

The most distinctive pathological changes are found in small arteries and arterioles, and are designated by a variety of terms dependent on morphology: hyaline or hyperplastic arteriolar sclerosis, fibrinoid degeneration or necrosis, lipohyalinosis and others. These terms are basically descriptive, but there are clinical correlations. For example, hyperplastic arteriolar changes are characteristically associated with malignant hypertension, whereas the hyaline form is usually found with slowly progressive hypertension of more moderate degrees and longer duration. There are, however, several authorities who question whether the vascular changes cause or result from the elevated pressure, although the preponderance of evidence clearly favors the latter.

For pathologists a diagnostic dilemma arises because morphologically identical vascular lesions may also be found in the absence of hypertension, and because vascular abnormalities may not be present in many patients with documented histories of notably elevated blood pressures.[42] It is most probable that duration and degree of hypertension are both critical to the induction of detectable lesions.

Nonetheless, the extent and severity of these vascular changes do provide postmortem evidence for preexistent hypertension. The kidney, an especially susceptible target organ, may have hyaline or hyperplastic arteriolosclerosis, or both. *Hyaline arteriolosclerosis* refers to the mural thickening caused by amorphous deposits that may represent proliferation of basement membrane material or precipitated plasma proteins (Figure 9). *Hyperplastic arteriolosclerosis* is characterized by the so-called onion-skinned pattern in which vessel lumina are narrowed by concentrically laminated spindle cells (possibly proliferating myoblasts or fibroblasts) admixed with collagen, elastin, lipids and reduplicated basement membrane. In some instances, a necrotizing vasculitis or fibrinoid necrosis may be evident in affected vessels, not only in the kidney, but in the brain and elsewhere.

Renal vascular embarrassment produced by these processes results in a galaxy of changes collectively designated *nephrosclerosis*. In the benign form with hyaline arteriolosclerosis, this is essentially the result of slowly progressive renal ischemia and is manifested by (1) periglomerular and interstitial fibrosis, (2) diffuse tubular atrophy

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and (3) glomerulosclerosis resulting from reduplicated basement membrane material in the intercapillary regions of the tufts. It is important to emphasize that these alterations are nonspecific and may occur simply as a consequence of age or other underlying disease processes, such as diabetes, even in the absence of hypertension. But such changes are consistently present if the patient has had significantly elevated blood pressure of sufficient duration.

In the malignant form of nephrosclerosis, the afferent arterioles and small arteries usually show the pronounced intimal hyperplastic alterations described previously. The hypoxia-sensitive proximal tubules may show degenerative changes, but because of the rapidly progressive nature of malignant hypertension, signs of ischemic atrophy and scarring in the glomeruli and interstitium are usually absent, unless there is superimposed benign nephrosclerosis. In addition to the proliferative vascular changes, there may be fibrinoid necrosis of arteriolar walls or frank necrotizing vasculitis affecting arterioles and glomeruli, with consequent petechial hemorrhages.

These pathological alterations usually associated with hypertensive states were not notably present in the kidneys of the patient in question. A few arterioles contained focal mural deposits (Figure 10), and a rare glomerulus was partially hyalinized; however, in general, the renal parenchyma appeared normal for the patient's age.

Much was made by counsel and witnesses for the plaintiff of certain terms in the autopsy report, generally lifted from context. For instance, "the thin [renal] capsule strips with difficulty from the granular surface" was taken as unequivocal evidence of significant nephrosclerotic changes; but obviously the term *granular* had been used by the pathologist in the visual not textural context, because microscopic review of random sections taken from both kidneys showed no pitting, irregularity, scarring or fibrosis. Additionally, the kidney weights of 140 and 160 grams (normal mean is 150 grams) showed that a diagnosis of ischemic atrophy was untenable.

The cursory microscopic descriptions in the autopsy report included the following statements: "hyalinized glomeruli are seen," and "[renal] arterioles have mild medial thickenings." Without regard to the magnitude of these changes, and declining to review the microscopic material, expert witnesses for the plaintiff again contended that this was unequivocal evidence for preexistent hypertension. This was eventually refuted by overcoming legal obstacles and introducing the microscopic slides per se as part of the complete autopsy record (as opposed to only the written report). By actual count, only five or six partially sclerotic glomeruli were present in nearly 1,000. Clearly, these were not the renal changes classically associated with chronic hypertension and nephrosclerosis.

The heart may provide additional evidence that antemortem hypertension existed. Like any muscle responding to the challenge of increased resistance, it adjusts to prolonged pressure elevations by hypertrophy, which in many instances may be massive (500 to 700 grams). Unless cardiac

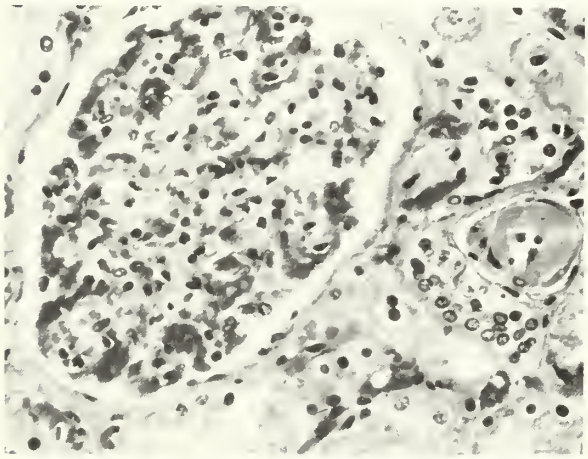

Figure 9.—Photomicrograph showing hyaline arteriolosclerosis in a patient with minimal hypertension. The arteriole to the right of the glomerulus shows eccentric mural thickening of a slight to moderate degree.

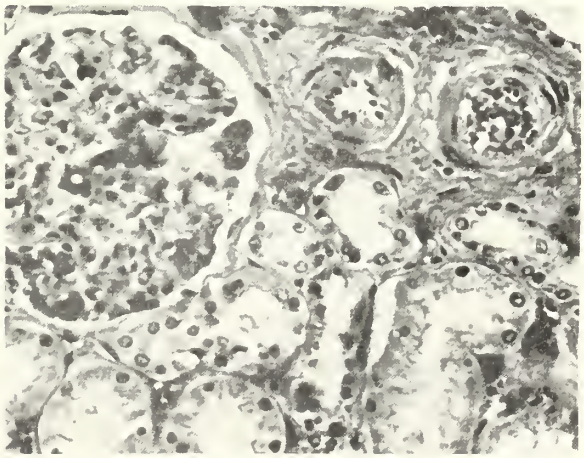

Figure 10.—Photomicrograph showing an example of the most severe arteriolar changes evident in the patient's kidneys. Small focal hyaline deposits are present in the arteriole adjacent to the glomerulus.

decompensation occurs, hypertrophy classically is limited to the left ventricle, the wall of which may be twice its normal thickness (greater than 2.5 cm), while the ventricular chamber is correspondingly diminished in capacity. The degree of hypertrophy seems more dependent on the level of systemic pressure elevations rather than on duration. Again, the pathological changes are nonspecific, and diagnosis of hypertensive heart disease is untenable if other possible causes of cardiac hypertrophy coexist. The patient in this case had a heart weight (360 grams) and left ventricular wall thickness (1.6 cm) that were at upper limits of accepted normal ranges. In actuality, the heart probably weighed less than reported, because it is standard practice at UCLA to leave portions of the great vessels attached. The gross impression of "mild hypertrophy" noted by the pathologist at the time of autopsy, therefore, was not supported, and there was insufficient hypertrophy to account for the left axis deviation shown by electrocardiography. In addition, there was only minimal evidence of atherosclerosis, a disease for which hypertension is a well-established predisposing condition.

The most important positive finding at autopsy was massive intracerebral hemorrhage primarily involving the left parieto-occipital region. The left cerebral hemisphere was edematous and swollen, and there were herniations of the cingulate and hippocampal gyri. Hemorrhage interrupted almost the entire internal capsule, communicated with the ventricular system and extended into the midbrain to the level of the pons. The arteries at the base of the brain were patent, regular in diameter, devoid of gross aneurysms and contained only an occasional small atheromatous plaque. In prolonged hypertension, even in the absence of atherosclerosis, these vessels often become tortuous and dilated, as do the vertebral and middle cerebral arteries.

Hypertension is the most common clinical condition associated with intracerebral hemorrhage. It is generally accepted that bleeding may originate from pressure-traumatized segments of congenital aneurysms, vascular anomalies or angiomas, or by rupture of one of multiple minute arteriolar aneurysms that occur in hyptertensive patients with extraordinarily high frequency. The pertinent question in this case—that is, was the bleeding a consequence of hypertensive vascular disease?—cannot be answered with certainty because of the limitations of standard autopsy procedures. The extensive hemorrhagic destruction of brain parenchyma (and poor fixation often caused by hemorrhage) may have obscured minute vascular abnormalities, but none were apparent. Charcot and Bouchard[31] were able to show microaneurysms of the penetrating arteries only after prolonged maceration of the brain parenchyma with running water and meticulous microscopic examination of the remaining vessel fragments. Such microaneurysms are usually less than 2 mm in diameter.[33] Green[43] and other investigators have used serial sectioning of multiple tissue blocks to find them; still others, including Ross-Russell[32] and Cole and Yates,[33] have resorted to postmortem microangiography and microdissections. With their painstaking technique, the latter authors were able to show a correlation between occurrence of microaneurysms and either preexistent hypertension or advancing age, but they also noted parenthetically that the number of microaneurysms found in any brain was directly proportional to the time spent looking for them. Such lesions are not likely to become apparent on routine autopsy without resort to extraordinary techniques.

Nevertheless, inferences may be made on the basis of changes in nonhemorrhagic portions of the brain. Hypertensive vascular disease in the cerebrum, as in other organs, is a generalized process and, therefore, should be detected if present. The microaneurysms associated with hypertension are unrelated to atherosclerotic fusiform or congenital saccular aneurysms. They characteristically occur in the smallest (less than 250 μ in diameter) penetrating arteries of the subcortical (especially posterior parietal) and basal ganglia regions. The putamen, globus pallidus and thalamus were the most frequent sites noted by Cole and Yates,[33] but they also found lesions in the caudate nucleus, internal capsule, pons and cerebellum. Histologic sections showed that the aneurysms were formed by disruption of the elastic lamina, destruction of smooth muscle media and coalescence of intima and adventitia into a saccular outpouching.[32,33] Hyaline thickening of the adjacent intima is common and may extend into the aneurysmal sac. Fibrinoid or lipoid material (lipohyalinosis) may also be present as transmural deposits.[32,44]

In addition to microaneurysms, another feature of hypertensive cerebral vascular disease is the presence of multiple, often cystic microinfarcts, principally in the basal ganglia and pons.[45] Such

"lacunar" infarcts occur secondary to occlusion of penetrating branches from the middle and posterior cerebral and basilar arteries,[46] and distinct clinical sequelae result.[47]

None of these characteristic lesions were identifiable in sections of brain tissue from this patient, nor was there any significant, nonspecific, arteriolar hyaline thickening. In conclusion, a review of the gross and microscopic findings in this case could not support pathological diagnoses of hypertensive nephropathy, cardiac disease or cerebral vascular disease.

Summary—The Role of the Expert Witness

MR. HUNT: Probably the most difficult case to defend, and by the same token the most frustrating experience for a doctor being sued for medical malpractice, is a case where there is no evidence of medical negligence. Unfortunately, there is no way a medical doctor can prevent being sued for malpractice. Any dissatisfied patient may sue a doctor. (In the case at hand, there was a verdict of 12 to 0 in favor of the defendant.) Although the defense verdict represents a victory, the residuals of that victory for the physician are lost time (six weeks to three months), sleepless nights, emotional outrage and defense costs ranging from $25,000 to $50,000.

The case came to trial because the plaintiff's expert witness questioned the standard care in the treatment of hypertension. This is the only evidence a jury may consider in evaluating the conduct of the treating physician.

As reported in the *California Book of Approved Jury Instructions,*[48] three key instructions to the jury bear on this standard of medical practice:

Duty of Physician and Surgeon[48(p176)]

In performing professional services for a patient, a physician or surgeon has the duty to have that degree of learning and skill ordinarily possessed by reputable physicians and surgeons, practicing in the same or a similar locality and under similar circumstances.

It is his further duty to use the care and skill ordinarily exercised in like cases by reputable members of his profession practicing in the same or a similar locality under similar circumstances and to use reasonable diligence and his judgment in the exercise of his skill and the application of his learning, in an effort to accomplish the purpose for which he is employed.

A failure to perform any such duty is negligence.

Medical Negligence—Standard of Care Determined by Expert Testimony[48(p201)]

You must determine the standard of professional learning, skill and care required of the defendant only from the opinions of the physicians and surgeons (including the defendant) who have testified as expert witnesses as to such standard.

You should consider each such opinion and should weigh the qualifications of the witness and the reasons given for his opinion. Give each opinion the weight to which you deem it entitled.

You must resolve any conflict in the testimony of the witnesses by weighing each of the opinions expressed against the others, taking into consideration the reasons given for the opinion, the facts relied upon by the witness, his relative credibility, and his special knowledge, skill, experience, training and education.

Alternative Methods of Diagnosis or Treatment[48(p180)]

Where there is more than one recognized method of diagnosis or treatment, and no one of them is used exclusively and uniformly by all practitioners of good standing, a physician and surgeon is not negligent if, in exercising his best judgment, he selects one of the approved methods, which later turns out to be a wrong selection, or one not favored by certain other practitioners.

In comparing the two sets of experts, the outstanding difference was the willingness of the defense physicians to acknowledge the existence of controversy and indecision in their own professional community. They stated that because of lack of unanimity of opinion as to what blood pressure ranges constituted borderline, mild or moderate hypertension, alternative avenues of diagnosis, care and treatment could be used. If there were a uniform selected blood pressure range for each category, there would still be differences of opinion as to when therapeutic agents should be used.

The plaintiff's expert witness stated that no such indecision or controversy existed in 1970 but, to the contrary, "every person with a blood pressure of 140/90 or more is hypertensive" and requires drug therapy. The defense witnesses convinced the jury that the defendant's course of treatment fell within one of several areas of standard accepted practice existing within the community. This case may have been lost had not the defense witnesses, by their dedication and forthright, objective approach, overcome the testimony of the plaintiff's physicians.

The role of the expert witness should not be that of an advocate who simply mimics or gives lip service to the plaintiff's theory of liability. Such a role reduces the physician professionally to the level of a "hired gun."

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Prophylaxis of Endocarditis During Surgical and Dental Procedures

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. NAUGHTON:* *In this Grand Rounds we will discuss the use of prophylactic antibiotics, a common and very controversial topic in the area of infective diseases. Dr. John Conte will review the prophylaxis of endocarditis during surgical and dental procedures.*

DR. CONTE:† Antibiotic prophylaxis involves the administration of an antibiotic in an attempt to prevent infection in an asymptomatic patient. This should be distinguished from empiric antibiotic therapy in which an antibiotic or combination of antibiotics is administered to a symptomatic patient in whom an infectious cause is suspected. These two concepts are often confused. This discussion focuses on the prophylactic administration of antibiotics to prevent infective endocarditis (IE) which may follow dental and other procedures.

In 1937 Burket and Burn[1] showed that pigmented *Serratia* painted on the gingivae of patients undergoing oral surgical procedures could be isolated from blood cultures shortly afterwards. The presence of *Serratia* bacteremia was confirmed in 18 of 90 patients studied. This was the first time that a direct link was provided between bacteria in the blood stream and bacteria in the gingival crevices.

In 1963 Angrist[2] hypothesized that various stresses lead to nonbacterial thrombotic endocarditis (NBTE), a lesion that occurs on the valve. The NBTE lesion is then colonized by bacteria from the blood stream, which leads to the development of infective carditis. Since that time numerous studies of IE using animals have been reported. Investigations on the pathogenesis of IE using these animals, particularly rabbits, have confirmed Angrist's hypothesis. Seeding of an abnormal heart valve by a bacteremia is the pathogenetic mechanism of IE associated with dental surgical procedures.

Recent studies by Sande and others[3] using electron microscopy have yielded remarkable pictures of the actual development of IE in experimental animals.

Does IE occur in association with dental procedures, and if so, what is the risk? There are numerous opinions in the literature. One author suggests that in one in 533 tooth extractions IE

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ABBREVIATIONS USED IN TEXT

AHA = American Heart Association
IE = infective endocarditis
NBTE = nonbacterial thrombotic endocarditis

results, another estimates it at one in 3,000 and yet another at one in 115,000 extractions. The consensus is that IE can occur following dental procedures but the exact risk is unclear.

It is estimated that as much as 15 percent of all cases of IE are related to dental surgical procedures.[4] However, this figure is controversial and dependent on the population studied. For example, if one studies the cases of endocarditis at San Francisco General Hospital, it is unlikely that 15 percent of them will be related to dental procedures.

One problem in correctly estimating the incidence of endocarditis associated with dental procedures is the uncertainty regarding the incubation period following the procedure. Starkebaum, Durack and Beeson[5] have reported the time between a dental procedure and the onset of symptoms in 76 cases of streptococcal endocarditis: Of the 76 cases, 64 occurred within two weeks of the procedure; a few cases occurred as long as two months later. The authors felt that in cases that occurred beyond two months, it was unclear as to whether the procedure could definitely be related to the development of IE.

Which are the procedures that may lead to bacteremia, thereby placing patients at risk for the development of IE? Everett and Hischman reviewed the relationship between dental extractions and bacteremia in six studies of adults and five of children.[6] Bacteremia was common, occurring in 18 percent to 85 percent of adult patients and 30 percent to 65 percent of children. Streptococci, diphtheroids, *Staphylococcus epidermidis* organisms and anaerobes were cultured in blood specimens of both the adults and children. Even though these data show that dental procedures regularly lead to bacteremia in adults and in chil-

TABLE 1.—*Dental Maneuvers* and Bacteremia†*

Procedure or Manipulation	*Cultures in the Blood*	
	Percent Positive	*Predominant Organisms*
Tooth rocking	86.0	*Streptococcus* sp, other
Brushing of teeth	24.2	*Streptococcus* sp
Chewing hard candy	17.4	*Staphylococcus epidermidis*
Periodontal operations (gingivectomy, osteoplasty, flap operation)	87.9	*Streptococcus* sp, diphtheroids, anaerobic mouth flora
Gingival resection	35.8	*Streptococcus* sp, *Staphylococcus aureus, S epidermidis*
Subgingival scaling		Not stated
Hand curets	66.7	
Ultrasonic instrument	79.2	
Chewing bubble gum	22.0	Not stated
Dental prophylaxis	28.0	Diphtheroids, anaerobic mouth flora
Oral irrigation device (mild gingivitis or less)	7.0	*Staphylococcus* sp, anaerobes
Oral irrigation device (severe gingivitis)	27.0	*Streptococcus* sp, *Staphylococcus* sp, diphtheroids, other

*Excluding extraction of teeth.
†Modified and abstracted from Everett and Hischmann.[6]

TABLE 2.—*Surgical Procedures or Manipulation of Airway Passages and Bacteremia**

Procedure or Manipulation	*Cultures in the Blood*	
	Percent Positive	*Predominant Organisms*
Tonsillectomy (3 series)	28-38	*Streptococcus* sp, *Staphylococcus aureus, Haemophilus* sp, diphtheroids
Nasal surgical procedures	11	*Streptococcus* sp, *Staphylococcus* sp
Orotracheal intubation (25 patients)	0	
Nasotracheal intubation (25 patients)	16	*Streptococcus* sp
Fiberoptic bronchoscopy	0	
Rigid bronchoscopy (52 patients)	15	*Streptococcus* sp, *Staphylococcus epidermidis,* Gram-negative rods
Fiberoptic bronchscopy (4 case reports)	..	*Pneumococcus* sp (2), *Pseudomonas aeruginosa* (2) (1 biopsy)

*Modified and abstracted from Everett and Hischmann.[6]

dren, a wide variety of other procedures also lead to this condition (Table 1).[6] For example, tooth rocking led to bacteremia in 86 percent of the patients in the series. The organisms were those that are ordinarily found in the normal oropharynx. Periodontal operations, particularly with osteoplasty or manipulation of the gingivae lead to a significant percentage of bacteremias. Table 2 illustrates that simple chewing of bubble gum or hard candy, brushing one's teeth, routine dental prophylaxis, and use of an oral irrigation device also lead to bacteremia in a significant number of patients.[6] In one report, however, bacteremia was not associated with routine dental prophylaxis.[7]

Surgical procedures or manipulation of the airway passages also leads to bacteremia with organisms commonly found in the normal oropharynx and nasopharynx[6] (Table 2). Orotracheal intubation seems to be safe, at least in the small series of patients reported.[8] However, nasotracheal intubation and suctioning were both associated with bacteremia in 16 percent of patients.[8] Fiberoptic bronchoscopy, initially reported as not leading to bacteremia, has subsequently been associated with bacteremia leading to metastatic infection. In two patients pneumococcal infections developed and in two others, *Pseudomonas* sp infection. The rigid bronchoscope was associated with bacteremia in 15 percent of patients.

The American Heart Association (AHA) has broadened its recommendation for prophylactic antibiotics to include gastrointestinal and surgical procedures.[9] Table 3 summarizes a variety of gastrointestinal and genitourinary procedures that have been associated with bacteremia. Esophageal dilatation with an unsterilized instrument, for example, led to positive cultures in all of 18 patients.

TABLE 3.—*Gastrointestinal (GI) and Genitourinary Procedures and Bacteremia*

Procedure and Reference No.	*Cultures in the Blood*	
	Percent Positive	*Predominant Organisms*
Esophageal dilatation		
Unsterile dilator (18 patients)[6]	100	*Staphylococcus aureus, S epidermidis*
Sterile dilator (12 patients)[6]	0	
Upper GI fiberoptic endoscopy (2 series) (no correlation biopsy)[6]	8.0-12.0	*Streptococcus* sp, *Neisseria* sp, *Staphylococcus epidermidis*, diphtheroids
Sigmoidoscopy (3 reports)[6]	0- 9.5	*Enterococcus* sp, Gram-negative rods
Colonoscopy (2 reports)[6]	2.5- 5.8	Alpha-hemolytic *Streptococcus* sp, *Entamoeba coli, Bacteroides* sp
Barium enema (175 patients)[12]	11.4	Anaerobic and aerobic Gram-negative rods
Liver biopsy (2 reports)[10,11]	2.9-13.5	*Pneumococcus* sp, Gram-negative rods, *Staphylococcus aureus, Streptococcus* sp, diphtheroids
Endoscopic retrograde cholangiopancreatography		
Unsuccessful (20 patients)	0	*Streptococcus faecalis, Pseudomonas aeruginosa, Entamoeba coli*
Successful (63 patients)[13]	7.9	
Routine rectal examination		
In 50 patients[14]	0	
In 74 patients[15]	4	Not stated

TABLE 4.—*Urethral and Urologic Manipulations and Bacteremia**

Manipulation	*Cultures in the Blood*	
	Percent Positive	*Predominant Organisms*
Urethral dilatation (3 reports) (without surgical procedure)	19-33	Gram-negative rods, *Enterococcus* sp
Cystoscopy (2 reports)	0-17	Gram-negative rods
Transurethral resection		
Sterile urine (102 patients)	10.8	Not given
Nonsterile urine (254 patients)	57.5	
Routine catheterization (75 patients)	8.0	Gram-negative rods, *Enterococcus* sp

*Modified and abstracted from Everett and Hischmann.[6]

However, in 12 other patients no cultures were positive when a sterile dilator had been used. Upper gastrointestinal fiberoptic endoscopy, colonoscopy and barium enema, ordinarily felt to be benign procedures, have all been associated with bacteremia in a significant number of patients. In two reports liver biopsies were associated with bacteremia in 2.9 percent and 13.5 percent of patients, respectively.[10,11]

Endoscopic retrograde cholangiopancreatography (ERCP) also has been associated with bacteremia.[13] Tsui and co-workers[13] reported bacteremia in 7.9 percent of patients in whom the duct was successfully cannulated, while in 20 patients in whom duct cannulation was unsuccessful, there were no positive cultures of blood specimens. The organisms that were recovered were all enteric aerobes. Gram-negative or anaerobic endocarditis following any of these procedures is rare, and one should not conclude that prophylaxis is necessary for all of these procedures. In fact, routine rectal examination has been associated with bacteremia in only 4 percent of patients in one report,[14] and 0 percent in another.[15]

Table 4 summarizes bacteremia associated with urethral and urologic manipulations.

What are the other possible portals of entry that might lead to bacteremia and IE? A surgical operation involving any infected site, any chronic infection such as osteomyelitis or urinary tract infection, or cutaneous infection associated with recurrent furunculosis or intravenous drug use may lead to bacteremia or IE. In approximately 50 percent of patients with IE the portal of entry is unknown.

Given the clinical procedures and situations that lead to bacteremia, what are the cardiovascular abnormalities that place patients at risk for

TABLE 5.—*Estimate of Risk of Infective Endocarditis Developing in Relationship to Underlying Conditions**

Relatively High Risk	*Intermediate Risk*	*Very Low or Negligible Risk*
Prosthetic valves	Mitral valve prolapse	Arteriosclerotic plaques
Arteriovenous fistulas	Tricuspid valve disease	Coronary artery disease
Hyperalimentation lines	Pulmonary valve disease	Atrial septal defects
Patent ductus arteriosus	Asymmetric septal hypertrophy	Cardiac pacemakers
Fallot tetralogy		Surgically corrected lesions (without prosthetic implants)
Ventricular septal defect		
Coarctation of the aorta		
Aortic valve disease		
Mitral valve disease		
Marfan syndrome		
Previous infective endocarditis		

*Reprinted with permission from Durack.[16]

TABLE 6.—*Antibiotic Regimens Ranked According to Efficacy in Prevention of Endocarditis in Experimental Animals**

	Regimens for Experiment Animals Injected With Infecting Agent	
Degree of Efficacy	*α-Hemolytic Streptococci*	*Enterococci*
Effective	Penicillin G plus streptomycin Repeated penicillin V with large loading dose Vancomycin	Ampicillin plus gentamicin Ampicillin plus streptomycin Vancomycin (high dose) Vancomycin (lower dose) plus streptomycin
Partially effective	Procaine penicillin G Repeated erythromycin Cefazolin plus streptomycin Streptomycin	Vancomycin (lower dose) Ampicillin Streptomycin
Ineffective	Ampicillin Penicillin G Penicillin V without loading dose Cefazolin, cephalexin Clindamycin Erythromycin Rifampin Tetracycline Trimethoprim-sulfamethoxazole	Gentamicin Cefazolin Cefazolin plus gentamicin

*Single doses were tested except where indicated.

the development of IE? Table 5 was compiled by Durack[16] and is a rough estimate of the risk of IE developing in relationship to various underlying conditions. In patients with prosthetic valves, arteriovenous fistulas and hyperalimentation lines the risk of infection developing is greatest. Patients with ventricular septal defects, aortic valve disease, mitral valve disease and previous IE are also at high risk. Patients with mitral valve prolapse, tricuspid and pulmonary valve disease and septal hypertrophy are judged to be at intermediate risk. In this regard the AHA recommends that patients with mitral valve prolapse receive prophylaxis only if mitral insufficiency is present. It is important to emphasize that patients with coronary artery disease, atrial septal defect (ASD), pacemakers or any surgically corrected lesion without a prosthetic implant are at low risk for the development of IE.

Where do most of the data come from regarding the prophylaxis of IE? The AHA recommendations are based largely on experiments in rabbits.[17-19] One can promote the development of endocarditis in rabbits by rather simple procedures.[20] A catheter placed in the right side of the heart through the jugular vein or into the left side of the heart through the carotid artery will produce a nonbacterial thrombotic endocarditic lesion within one to three days. Intravenous injection of a microorganism such as *Streptococcus viridans* or *Candida,* will lead to IE in most or all of the animals. One can simulate the clinical situation in a dental or other surgical procedure by injecting a variety of antibiotics into the animal just before injection of the test organism. The ability of each antibiotic, or combination of antibiotics, to prevent IE can be estimated from this model.

What will be the results if one carries out this experiment, using a penicillin-sensitive streptococcal organism and a variety of antibiotics that are clinically available? Bacteriostatic antibiotics do not prevent IE in this situation.[17] Tetracycline in doses equivalent to those used in adults is ineffective. The same is true for erythromycin. This observation is noteworthy because erythromycin appears in the American Heart Association's recommendations for prophylaxis in patients allergic to penicillin. Clindamycin and chloramphenicol are also ineffective.

What antibiotics do work? Penicillin G and other bactericidal antibiotics are effective. However, because of its short half-life, aqueous penicillin G alone was ineffective for prophylaxis; thus, in 19 of the 21 animals IE developed.[17] This is probably due to the fact that the "area under the curve" is not great enough because of the rapid elimination of penicillin G. Therefore, the AHA recommends combining penicillin G with procaine penicillin to prolong levels in the blood. Ampicillin, cephalosporins, trimethoprim-sulfamethoxazole and rifampin are ineffective. Streptomycin alone confers some protection. Combinations of antibiotics which include vancomycin, penicillin or ampicillin plus an aminoglycoside confer the greatest protection. These observations are based on experiments performed with penicillin-sensitive *Streptococcus viridans.* The conclusion from this series of experiments is that short-term concentrations of penicillin G in the blood, even when the drug is given in large doses, are ineffective. However, procaine penicillin G alone in high doses or with penicillin G is effective. In penicillin-allergic patients, vancomycin is the best alternative.

The same experiment with rabbits using *S faecalis* as the infecting agent, would be more pertinent to the evaluation of prophylaxis for genitourinary and gastrointestinal tract proced-

TABLE 7.—*Prophylaxis for Dental Procedures and Surgical Procedures of the Upper Respiratory Tract in Relation to Underlying Conditions**

	Indications for Prophylaxis	
Procedure	*Most Congenital Heart Diseases,† Rheumatic or Other Acquired Valvular Heart Disease; Idiopathic Hypertrophic Subaortic Stenosis; Mitral Valve Prolapse Syndrome With Mitral Insufficiency‡*	*Prosthetic Heart Valves§*
All dental procedures that are likely to result in gingival bleeding°	Regimen A or B	Regimen B
Surgical procedure or instrumentation of the respiratory tract¶	Regimen A or B	Regimen B

*Modified from Kaplan.[9]

†Ventricular septal defect, tetralogy of Fallot, aortic stenosis, pulmonic stenosis, complex cyanotic heart disease, patent ductus arteriosus or systemic to pulmonary artery shunts. Does not include uncomplicated secundum atrial septal defect.

‡Although cases of infective endocarditis in patients with mitral valve prolapse syndrome have been documented, the incidence appears to be relatively low and the necessity for prophylaxis in all of these patients has not yet been established.

§Some patients with a prosthetic heart valve in whom a high level of oral hygiene is being maintained may be offered orally administered antibiotic prophylaxis for routine dental procedures. However, the following parenterally given antibiotics are recommended for patients with prosthetic valves who require extensive dental procedures, especially extractions, or oral or gingival surgical procedures.

°Does not include shedding of deciduous teeth or simple adjustment of orthodontic appliances.

¶Tonsillectomy, adenoidectomy, bronchoscopy, and other surgical procedures of the upper respiratory tract involving disruption of the respiratory mucosa.

ures.[19] Administration of ampicillin alone is only partially effective in preventing IE in this situation. Addition of an aminoglycoside to ampicillin improves the results but protection is still not complete. Vancomycin alone is as effective as ampicillin plus an aminoglycoside. Table 6 ranks the efficacy of various antibiotic regimens in this same experiment.[16] Administration of ampicillin or penicillin G, with an aminoglycoside, vancomycin alone in high doses or a lower dose with an aminoglycoside are effective in offering protection. Gentamicin alone, the cephalosporins and any of the bacteriostatic antibiotics would be expected to be ineffective.

Recommendations regarding prophylaxis for dental procedures and surgical procedures of the upper respiratory tract are summarized in Table 7. The AHA advises that prophylaxis be given to patients with congenital heart disease (except ASD), rheumatic or other acquired valvular disease, idiopathic hypertrophic subaortic stenosis, and mitral valve prolapse with mitral insufficiency. Regimen A is a combination of aqueous penicillin and procaine penicillin followed by penicillin V (formerly called phenoxymethyl penicillin) in a

TABLE 8.—*Antibiotic Regimens for Dental Procedures and Surgical Procedures of the Upper Respiratory Tract**

Regimen A: Penicillin

Combined Parenteral and Oral Administration:

Adults: Give aqueous crystalline penicillin G (1,000,000 units intramuscularly) *mixed with* procaine penicillin G (600,000 units intramuscularly) 30 minutes to an hour before the procedure, and then give 500 mg of penicillin V (formerly called phenoxymethyl penicillin) orally every six hours for a total of eight doses.†

Oral Administration:‡

Adults: Give 2 grams of penicillin V orally 30 minutes to an hour before the procedure and then 500 mg orally every six hours for a total of eight doses.†

For Patients Allergic to Penicillin:

Use either Vancomycin (see Regimen B)

or

Adults: Give 1 gram of erythromycin orally 1½ to 2 hours before the procedure and then 500 mg orally every six hours for a total of eight doses.†

Regimen B: Penicillin plus Streptomycin

Adults: Give aqueous crystalline penicillin G (1,000,000 units intramuscularly) *mixed with* procaine penicillin G (600,000 units intramuscularly), *plus* 1 gram of streptomycin 30 minutes to an hour before the procedure, and then 500 mg of penicillin V orally every six hours for a total of eight doses.†

For Patients Allergic to Penicillin:

Adults: Give 1 gram of vancomycin intravenously over 30 minutes to an hour. Begin initial infusion of vancomycin 30 minutes to an hour before the procedure. Then give 500 mg of erythromycin orally every six hours for a total of eight doses.†

*Modified from Kaplan.[9]

†In unusual circumstances or in the case of delayed healing, it may be prudent to provide additional doses of antibiotics even though available data suggest that bacteremia rarely persists longer than 15 minutes after the procedure. A physician or dentist may also choose to use the parenteral route of administration for all of the doses in selected situations.

‡For those patients receiving penicillin orally every day for secondary prevention of rheumatic fever, alpha-hemolytic streptococci which are relatively resistant to penicillin are occasionally found in the oral cavity. While it is likely that the doses of penicillin recommended in regimen A are sufficient to control these organisms, a physician or dentist may choose one of the suggestions in Regimen B or may choose to administer erythromycin orally.

TABLE 9.—*Antibiotic Regimens for Gastrointestinal and Genitourinary Tract Surgical Procedures and Procedures Involving Use of Instruments*†*

Adults: Give aqueous crystalline penicillin G (2,000,000 units intramuscularly or intravenously), *or* ampicillin (1 gram intramuscularly or intravenously) *plus* gentamicin (1.5 mg per kg of body weight, but not to exceed 80 mg intramuscularly or intravenously), or streptomycin (1 gram intramuscularly). Give initial dose 30 minutes to an hour before the procedure. If gentamicin is used then give a similar dose of gentamicin and penicillin (or ampicillin) every eight hours for two additional doses.‡ If streptomycin is used then give a similar dose of streptomycin and penicillin (or ampicillin) every 12 hours for two additional doses.‡

For Patients Allergic to Penicillin‡

Adults: Give vancomycin (1 gram intravenously over 30 minutes to an hour) *plus* streptomycin (1 gram intramuscularly). A single dose of these antibiotics given 30 minutes to an hour before the procedure is probably sufficient, but the same dose may be repeated in 12 hours.‡

*Modified from Kaplan.[9]

†In patients with significantly compromised renal function, it may be necessary to modify the dose of antibiotics used. Some of these doses may exceed manufacturer's recommendations for a 24-hour period. However, because they are only recommended for a 24-hour period in most cases, it is unlikely that toxicity will occur.

‡During prolonged procedures, or in the case of delayed healing, it may be necessary to provide additional doses of antibiotics. For brief outpatient procedures such as uncomplicated catheterization of the bladder one dose may be sufficient.

TABLE 10.—*Genitourinary and Gastrointestinal Tract Procedures Included for Prophylaxis*

Urethral catheterization
Cystoscopy
Sigmoidoscopy with biopsy
Hepatobiliary surgical procedures
Septic abortion and peripartum sepsis

TABLE 11.—*Genitourinary and Gastrointestinal Procedures Not Included for Prophylaxis*

Uncomplicated vaginal delivery
Upper gastrointestinal endoscopy with biopsy
Percutaneous liver biopsy
Proctosigmoidoscopy
Barium enema
Dilatation and curettage (D&C) and routine pelvic examination
Uncomplicated insertion or removal of intrauterine device

dosage of 500 mg four times per day for a total of eight doses. Regimen B combines regimen A with streptomycin (Table 8). Because patients with prosthetic heart valves are at such high risk, regimen B is recommended in all cases. Procaine penicillin G is included in both regimens to yield a greater "area under the curve" as previously discussed. One can use an orally given regimen by replacing the procaine penicillin in regimen A with 2 grams of penicillin V given 30 minutes to an hour before the procedure. There is no version of regimen B that can be administered orally. A prophylactic drug regimen given orally may not be as effective as one given parenterally; therefore, in high-risk patients regimen B is recommended. In patients who are allergic to penicillin, vancomycin followed by erythromycin is recommended. Based on the data from the animal experiments previously discussed, the effectiveness of erythromycin for prophylaxis is doubtful. However, it is the best alternative available for penicillin-allergic patients. Vancomycin given orally is not absorbed and should not be used.

For patients taking penicillin every day for secondary prophylaxis of rheumatic fever, regimen A will probably be effective. However, because organisms that are relatively resistant to penicillin may be found in the oropharynx of these patients, regimen B or an erythromycin regimen would be a wiser choice. In gastrointestinal and genitourinary tract surgical procedures or those involving use of instruments, the AHA recommends administration of penicillin or ampicillin with an aminoglycoside, either streptomycin or gentamicin (Table 9). All drugs are given parenterally and are repeated twice for a total of three doses. In patients allergic to penicillin, vancomycin is substituted for penicillin or ampicillin. Streptomycin or gentamicin is still included in the regimen even if vancomycin is used. Table 10 lists those procedures for which prophylaxis is recommended and Table 11 summarizes those procedures for which prophylaxis is specifically excluded.

I wish to conclude this discussion with the American Heart Association's own disclaimer: Since there have been no controlled trials, adequate data for comparing various methods for prevention of endocarditis in man are not available. However, an experimental animal model permitting consistent induction of bacterial endocarditis with microorganisms which often cause the infection in man has allowed experimental evaluation of both prophylaxis and treatment. Data from these studies although derived from animal rather than clinical investigations, represent the only direct information on efficacy of prophylaxis that is presently available. This information has influenced formulation of the current recommendations. The significant morbidity and mortality associated with infective endocarditis and the paucity of conclusive clinical studies emphasize the need for continuing research into the epidemiology, pathogenesis, prevention, and therapy of infective endocarditis.[9]

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Important Advances in Clinical Medicine

Epitomes of Progress — Occupational Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in occupational medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in occupational medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Occupational Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Skin Absorption of Toxic Materials

SOME 20 YEARS AGO the toxicologic literature posed the following question: Are chemicals that are applied to the skin likely to be absorbed? At that time it was assumed that the outermost layer of the epidermis, the stratum corneum, presented an almost impermeable barrier to most chemicals; absorption was believed to be the exception rather than the rule.

In the last ten years, however, the situation has reversed, largely because of improved analytic methods (the most convenient of which uses radioactively labeled compounds). It has become clear that the opposite is true. Most materials with small molecular weights can be absorbed by the skin. The question now is not *whether* but *how much* of a material will be absorbed, and what are the kinetics involved. It can be assumed that many, if not most, of the organic compounds routinely handled by people in industry and in cosmetics (such as skin care products, topical drugs and home care products) are absorbed percutaneously. Even substances with relatively high molecular weights, such as tuberculin protein, are absorbed sufficiently to allow a positive tuberculin test by epicutaneous application.

The clinical significance of this absorption may be overt or covert, depending on many factors in a patient's history and awareness on the part of the clinician. Two recent examples involved hexachloraphene, and phenolics used in laundering hospital linen. Ordinarily, hexachloraphene is not extensively absorbed by the skin. However, in cases in which it comes into contact with more permeable areas such as the face, is in continuous contact with the skin for an extended time (for example, due to its use with diapers) or has enhanced permeability due to abnormal skin conditions, significant levels may be detected in the blood and tissues. Thus, fatalities occurred as a result of high concentrations of hexachloraphene present in a baby powder formulation manufactured in France. Here in the United States an equally challenging epidemiologic problem arose. A careful investigation of deaths of infants in several hospital nurseries traced the cause to absorption of phenolics from crib linens.

We are only beginning to recognize and solve the problems within this important clinical area. Therefore, some practical guidelines for physicians in treating patients who may be suffering from absorption of toxic materials are needed. First, it is necessary to determine whether percutaneous penetration is a possible route of toxic exposure. Second, it is important to search the

literature and to ask the supplier of the material in question whether absorption studies using appropriate methods have been done. Using these lines of inquiry one may be able to determine the site and manner of entry.

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Wester R, Maibach HI: Percutaneous absorption in man and animal—A perspective. *In* Drill VA, Lazar P (Eds): Cutaneous Toxicity. New York, Academic Press, 1977, pp 111-126

Asbestos-Related Diseases

BECAUSE OF EPIDEMIOLOGIC STUDIES on the pathological changes produced by inhalation of free asbestos fiber, it is now known that the primary diseases among asbestos workers are asbestosis and cancer. Although cancer may develop at different sites in these exposed persons, approximately 20 percent of all deaths are due to lung cancer. Some 6 percent to 7 percent result from pleural or peritoneal mesothelioma, or both, and an excess of deaths is found in several other categories of malignant disease, specifically cancer of the esophagus, stomach, colon-rectum, oropharynx, larynx and kidney. In a study of 17,800 asbestos insulation workers followed from January 1, 1967, to January 1, 1977, it was predicted statistically that 1,661 deaths would occur; however, 2,270 were observed. Of these, 994 deaths resulted from cancer, although only 320 had been expected. No cases of mesothelioma were anticipated because of the rarity of this tumor; however, in the group studied, there were 175. Asbestosis, without malignant change, accounted for 162 deaths.

Mesotheliomas, even though rare, were also encountered among family contacts of asbestos workers residing in the same households, in addition to persons living within a quarter mile or so of facilities where asbestos-containing materials were used. It is important to note that while mesothelioma is not necessarily the most common disease following asbestos exposure, it provides an extremely useful index because it is not known to be found in relation to other types of exposure.

There is a 15- to 35-year lag period between initial contact with asbestos and clinical evidence of involvement. Radiographic changes may appear earlier, although in workers with 5 to 15 years of exposure, there are usually no symptoms and no disability, even with the changes visible by x-ray study. Typical of the disease is the increase in abnormal findings in direct relationship to length of exposure after initial contact. Further, early studies in shipyards indicated that members of other crafts such as boilermaking, shipfitting, welding, and the like also showed symptoms of mesotheliomatous disease. During World War II approximately 4.5 million men and women were employed in shipyards in the United States, and since then, the number has fluctuated between 200,000 and 250,000. Because of the turnover, the actual number of persons exposed is larger. Of interest is the finding that just one month of employment has led to increased risk of death from cancer.

Subsequent studies of shipyard personnel elsewhere have substantiated earlier findings. At one site, approximately half of the workers examined showed radiographic evidence of pulmonary and pleural changes usually seen following direct or indirect exposure to asbestos. Among persons with longer work experience there was a higher incidence of pleural asbestosis and parenchymal disease. The nature of shipyard work exposes all types of personnel to asbestos during installation, repair or removal of asbestos-containing materials. The extent of risk, that is, the number of neoplasms that will occur in the future among workers in whom there is evidence already of asbestotic changes, is not known.

The following procedures are recommended: (1) Make workers and managerial personnel aware of the disease potential of past and future exposure to asbestos; (2) avoid additional exposure through appropriate industrial engineering and industrial hygiene controls; (3) institute prompt therapy for respiratory infections that occur in asbestotic patients; (4) diagnose as early as possible cases of lung cancer in worker-patients manifesting radiographic changes and having a history of cigarette smoking; (5) exert every effort to have those exposed to asbestos stop smoking—not only to avert pulmonary carcinoma, but to diminish serious pulmonary disabilities associated with fibrosis of the lung, and to lessen the chance of the development of esophageal malignancy, and finally (6) through education, prevent workers from contaminating their homes with asbestos-soiled work clothing or tools.

The National Cancer Institute has mounted a strong educational campaign for the medical profession, workers and the lay public. Many ma-

terials formerly containing asbestos have been replaced by substitutes. Still to be accomplished, however, is acceptance by primary care physicians that asbestosis is a potentially dangerous precancerous pulmonary disease even though a patient may be asymptomatic and feeling no symptoms of disability. Also physicians should observe workers who are exposed to *any* fibrous material. Carrying out periodic medical surveillance measures such as chest radiography, pulmonary function evaluation and physical examination in persons exposed to asbestos must become a way of life in these physician-patient relationships.

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Low Level Radiation Exposure

THE DANGERS AND EFFECTS of carrying out diagnostic x-ray examinations in humans require consideration of possible genetic and somatic risks. The genetic risk, less than the somatic risk, is small, and can be decreased by the use of gonadal shielding whenever possible. Protection of the ovaries, especially in women who are potential child-bearers, is carried out by shielding the pelvic cavity. Gonadal protection in males involves shielding the pelvic area except for the symphysis pubis.

What is the genetic risk? The best current estimates of hypothetical risk of an observable abnormality in a fetus from diagnostic radiation does not exceed 1 to 5 in a 1,000 rad-absorbed dose (the dose from 1,000 separate films of the abdomen). This is substantially less than the natural (cosmic-ray induced) incidence of 40 birth defects in 1,000 infants with birth anamolies who have not been exposed to diagnostic x-rays prenatally. The extra risk from diagnostic radiation, which in most instances is nowhere near 1,000 rads, is therefore negligible. Furthermore, it is not possible to state which observable birth anomaly may have been caused by cosmic radiation and which one may have been caused by diagnostic x-ray examinations.

The somatic risk of diagnostic x-ray examinations is easier to quantitate. This risk can be divided into two parts: prenatal exposure due to abdominal or pelvic study in a pregnant woman and postnatal exposure.

In cases of prenatal exposure, the third to sixth gestational weeks are probably the most critical; therefore, x-ray examinations should not be done during the first trimester of pregnancy. The guideline for exposure of fertile women to radiation indicates that the use of x-ray examinations should be determined on an individual basis. Concern over harmful effects should not prevent the proper use of radiation procedures when significant diagnostic information can be obtained.

The risk from postnatal exposure is limited to the carcinogenic effects due to diagnostic x-ray examinations. Children have an enhanced sensitivity to radiation compared with adults, but also require less exposure to produce a desired radiograph. Therefore, the risk estimates might be similar.

The dose from two x-ray films of the chest is approximately 45 mR. The chance of cancer developing in the area of the chest without extra radiation exposure is 1.5 in a million. Thus, a patient would have to undergo 1,950 x-ray examinations of the chest to increase his risk factor by 10 percent.

Xeromammography with two films of the breast gives an approximate skin dose of 2,000 mR. In a patient 35 to 50 years old there are 66 chances in a million that carcinoma of the breast will develop without mammograms, due to the known latency period for the cancer under consideration, which is generally taken to be 10 to 25 years. This patient would have to undergo 41 mammographic examinations to increase the risk factor by 10 percent. Therefore, it is apparent that the risk of carcinoma of the breast developing in women without x-ray examinations as a factor is significantly greater than the risk created by the exposure to radiation from the mammogram. However, we feel that in women under 34 years of age xeromammography should be done only if there is a strong family history of breast cancer, or indication of a lesion such as a suspicious breast lump. Routine xeromammography for women older than 34 years is recommended because the risk from the radiation is significantly decreased.

As can be seen, in most cases the risk from x-ray examinations is small, on the order of a few chances in a million for each examination. This

is roughly the same as the chance of being killed on a coast-to-coast plane ride on a regularly scheduled airline.

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Asymmetrical Hearing Loss

IT IS BELIEVED that between 5 and 6 million industrial workers in the United States have suffered serious loss of hearing from exposure to noise in the workplace. A hearing defect is usually defined as an average hearing loss of greater than 25 dB at frequencies of between 500 and 2,000 Hz. Some 10 percent of industrial workers in this country meet this criterion. The number would be increased to 50 percent if the definition included hearing losses at frequencies above 2,000 Hz. Among patients referred for assessment of compensation for presumed industrially-induced hearing losses, 15 percent have been found to suffer from unilateral or asymmetrical sensorineural hearing loss, with an average difference in hearing threshold between the two ears of 15 dB at frequencies of 500, 1,000 and 4,000 Hz. This condition should be investigated because it may be the first symptom of a variety of cochlear disorders or, more seriously, of retrocochlear disorders such as acoustic neuroma or a posterior fossa tumor.

In assessing the cause of asymmetrical hearing loss, several audiologic and otologic tests are done, including such conventional tests as air and bone conduction audiometry, stapedius reflex threshold estimation, reflex decay, speech reception threshold and speech discrimination and, in some cases, evoked response audiometry. Temporal bone tomograms are conducted to show the internal auditory meatus. Vestibular tests are often carried out as well. Any significant or unexplained abnormality is evaluated further by neurological examination, computerized axial tomographic (CAT) scanning or myelogram, or with repeated vestibular and hearing tests.

One major study of asymmetrical hearing loss attributed the cause to noise exposure in 34.5 percent of the cases reviewed. Three sources of asymmetrical loss of hearing in the workplace were proposed: (1) a sudden loud noise such as an explosion, which produced a massive loss of hearing in both ears, one of which recovered while the other did not; (2) a well-documented history of greater exposure to noise by one ear than the other, as, for example, the employee driving a tractor with one ear turned toward the exhaust, and (3) different sensitivity of the ears to the same sound, producing similar audiometric patterns but at different levels.

Even after considerable investigation, the yield of useful information on this condition is low. In a recent study, 108 patients were evaluated extensively for hearing loss: 87 underwent vestibular tests, 85 had internal canal tomograms done, 12 had myelograms done and 16 had brain scans. No treatable disorders were discovered. Thus, the cause appears to be noise exposure.

In view of the large number of potential cases of asymmetrical hearing loss and the apparent rarity of acoustic neuroma or angle tumor, the high cost of finding a single tumor may be prohibitive. On the basis of recent experience, a reasonable recommendation may be that in unexplained asymmetrical hearing thresholds, otologic and audiologic consultations should be obtained, as well as vestibular tests, x-ray studies of the temporal bone and advanced hearing tests as indicated. If the results of these tests offer no indication of a central pathological condition then neither CAT scans nor myelograms are recommended on a routine basis.

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Occupational Histories in Medical Care

IN THE 1700's Bernardino Ramazzini told us as physicians to ask one more question: "What is your work?" Today, this question is no longer adequate. From many points of view, a much more complete occupational history is recommended—for the protection of workers, management and physicians alike.

The relation of present findings to past occupations may be crucial. An expanding knowledge of occupationally related carcinogenesis rests on sound data regarding work exposures. Smoking patterns and avocations should also be included.

Various occupational risks affecting male and

female gonadal systems (for example, risk of radiation exposure) are becoming better known. Workers should be advised of these risks for protection of their own health and, especially, the protection of pregnant women, particularly in the first trimester. Workers should also be advised of how continued work exposure might affect their future children.

Inadequate data regarding an employee's occupational record on the medical history may become the basis of negligence actions, and possibly cause for malpractice action. Physicians may not recognize how work exposures affect a patient's health. Nevertheless they should record all known work exposures (beginning with the most recent) and their place, duration, kind and so forth. Physicians in industrial areas should be aware of the characteristic work problems of the area.

The 1978 American Public Health Association (APHA) Policy Statement calls for the Department of Health, Education and Welfare (HEW) to initiate improvement of occupational history taking, and the proposed California State Health Plan of 1980 to 1985 calls on "providers" to develop occupational history forms. However, the taking of an occupational history is highly individual and time consuming, and the information is, at best, often uncertain. At least, if asked, the patient may remember if co-workers voiced health complaints. The complete occupational history has assumed new importance for good medical care both in and out of industry.

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EDITORIALS

'Hired Guns' in Court

FOR BOTH DOCTORS and lawyers their professional expertise is their stock in trade. They sell it in exchange for professional fees, offer it in return for a retainer or salary, or sometimes contribute it gratis to some worthy cause. But the expertise is quite different for a doctor and for a lawyer. Each discipline has a very different frame of reference and each has a very different approach to getting at the truth. Since courts are the turf of lawyers it is not unusual for doctors, whether wittingly or otherwise, to find themselves and their medical expertise being used as instruments of the legal expertise of the lawyers. Because each discipline tends to seek truth and recognize it differently, the whole truth as seen by the doctor may be eluded or evaded by the manipulations of expert lawyers in behalf of either plaintiff or defendant or both.

The Specialty Conference elsewhere in this issue draws attention to the role of an expert medical witness in court. The term "hired guns" is used to describe qualified expert medical witnesses who will give expert testimony to support the cause of the plaintiff or defendant as the case may be, and for a fee or not as the case may be. And too often there is a disquieting spectacle of a number of qualified medical experts giving quite different opinions based upon what appears to be much the same information. While all of this is cricket as the game is played in the adversary framework of a trial in court, often it seems to fall somewhat short of presenting the judge or jury with all the medical information needed, in a way which will help them to make the fairest and most correct decision.

One cannot help but be reminded of the quite recently established legal doctrine of informed consent. Here the decision maker is the patient, rather than a judge or jury, and the doctrine calls upon the physician to fully inform the patient of all the medical options, and of the pros and cons of each, so that he or she may make a fully informed decision. A parallel to the decision makers in a court trial seems obvious. The role of the expert medical witness should be less that of a "hired gun" for the plaintiff or defendant, and more that of a physician with the professional expertise to present to the court the current state of the art and science of medicine with respect to the problem at hand. This having been done, the court would then be in a position to make a truly informed decision much as a patient should be able to under the doctrine of informed consent.

Could it be that the time has come to apply the basic principle of full disclosure of the current state of the art and science of medicine (which underlies the concept of informed consent) to the role of the expert medical witness in a court of law? If this were done the truth, as it is understood in the discipline of medicine with respect to any given issue, could be more fully and accurately presented within the adversary framework of a courtroom trial, including full disclosure where there is difference of opinion—and the need for "hired guns" in court might actually become a relic of the past.

—MSMW

Clostridium difficile: A New Enteric Pathogen

ELSEWHERE IN THIS ISSUE, W. Lance George has nicely summarized recent data implicating *Clostridium difficile* as the cause of antibiotic-associated pseudomembranous colitis (PMC). PMC is regarded as an infrequent but serious adverse drug reaction, and has been studied extensively for more than three decades. Earlier work sug-

gested that *Staphylococcus aureus* was responsible. However, a critical review of the data indicates that either the role of this microbe was poorly documented or the disease reported at that time was different than PMC as it is encountered today.

How did this pathogen escape detection until the recent flurry of reports provided compelling evidence and confirmatory observations? The most plausible explanation is that fecal flora is simply too complex to detect a unique component unless there are clues to suggest specific microbes. Therefore, initial studies were done in animals with the objective of identifying a transferable toxin neutralized by clostridial antitoxins. This permitted a focus of attention on clostridia and led to the identification of *C difficile* as the cause of antibiotic-induced colitis. The first clinical application of the data from the studies in animals appears to have been in June 1977, when tests of stool specimens from a patient with lethal PMC showed the presence of both *C difficile* and its cytotoxin.

Subsequent studies have dealt with the incidence of this microbe and its toxin in stool specimens from additional patients, including various control subjects. Several important observations have emerged, based on data from several different laboratories. First, tissue cultures from nearly all patients with antibiotic-associated PMC have a cytopathic toxin that is neutralized by *C sordellii* antitoxin. The incidence of the toxin in patients with antibiotic-associated diarrhea, and in whom either symptoms are minor or there are no abnormalities shown on endoscopic examination, is approximately 20 percent. A common mechanism, therefore, is implicated in the entire spectrum of diarrheal complications ascribed to antimicrobials, although in many patients with less serious forms of the disease other causes seem to be involved. A second important observation from this subsequent work is that the role of *C difficile* as an enteric pathogen is limited almost exclusively to the presence of antimicrobial exposure. Available evidence indicates that *C difficile* plays no established role in other diarrheal conditions such as idiopathic inflammatory bowel disease, irritable bowel syndrome, ischemic colitis or neonatal necrotizing enterocolitis.

Another issue concerns the evidence that *C difficile* is responsible for the cytotoxin found in specimens of stool. As noted by George, the fact that *C sordellii* antitoxin neutralizes this cytotoxin initially suggested the presence of an alternative agent. However, *C sordellii* was not found with stool cultures, it failed to reproduce the colonic lesion with intracecal injection in animals, and in vitro studies with test strains did not show typical cytopathic changes in tissue culture. By contrast, *C difficile* satisfies all these criteria. Especially important was the observation that the cytotoxin produced by *C difficile* is neutralized by *C sordellii* antitoxin, indicating antigenic cross-reactivity. Studies to detect other clostridial species that produce an antigenically related cytotoxin have been unrewarding. These findings, coupled with stool culture results, suggest that detection of this cytotoxin is virtually diagnostic for the presence of *C difficile*.

The identification of a bacterial pathogen led to therapeutic trials using orally given vancomycin. This agent was attractive theoretically because it is active against virtually all strains of *C difficile*, there is minimal absorption so that levels in the colon are extremely high and there is essentially no reported toxicity with oral administration. The first trials, reported in 1978, showed that in nearly all patients there was a prompt and often dramatic response to treatment. Therefore, within 18 months the cause of PMC had been clarified, a sensitive and specific tissue culture assay to detect *C difficile* cytotoxin had been developed, and clinical trials had been done that established the efficacy of treatment with orally given vancomycin. Despite this progress, several practical facets of the problem require further study.

It should be emphasized that *C difficile* and its cytotoxin have been implicated in most or all cases of PMC. However, other mechanisms must be involved in many patients with antibiotic-associated diarrhea, including some who have serious forms of colitis or debilitating diarrhea without pseudomembrane formation. What approach should be taken, then, when it appears a patient may have *C difficile*-induced enteric disease? The first point to emphasize is recognition. The diagnosis should be considered whenever diarrhea develops in a patient either during or up to four weeks after administration of antibiotics. The role of endoscopy in evaluation is somewhat enigmatic. This procedure has revolutionized anatomical studies of the colon, as well as knowledge about diarrheal complications of antimicrobials. However, it is expensive and unpleasant. Moreover, sigmoidoscopy fails to detect rare cases in which lesions are restricted to the right colon, typical plaques

may be easily overlooked unless special precautions are taken and *C difficile* may be responsible for diarrhea even in the absence of demonstrable pseudomembranes. It is my impression that the tissue culture assay of stool is more important because it provides a causative mechanism which can be used as a rationale for therapeutic decisions regardless of pathological changes. Unfortunately, most clinical laboratories do not carry out tissue cultures, and there are only a small number of laboratories with tissue culture facilities that routinely do the test required to detect *C difficile* cytotoxin.

An alternative approach is testing stool specimens for fecal leukocytes, which are noted in most cases of *C difficile*-induced disease, although this finding is nonspecific. Gram stains are unlikely to be revealing because quantitative cultures indicate that the responsible pathogen usually accounts for a relatively small fraction of the flora that can be cultivated. Few laboratories are prepared to culture stool for *C difficile,* and detection of toxin is considered far more specific. Because the toxin has now been purified, it is likely that immunologic assays, which are more practical for routine laboratory use, will be forthcoming. In the meanwhile, most practicing physicians are forced either to rely on endoscopic studies and certain empiric decisions, or to resort to tissue cultures at a reference laboratory which may be some distance away.

Another question in management concerns indications for choosing a specific form of therapy—either administration of vancomycin to inhibit the pathogen or cholestyramine to bind the toxin. Experience has taught that in many patients with mild disease there will be spontaneous resolution of symptoms if the implicated drug is simply discontinued. The most clearly defined indications for therapy are persistent diarrhea or severe symptoms. Cholestyramine has the advantage of being relatively cheap and having documented efficacy, although collective experience shows that it is not as predictably effective as vancomycin. Vancomycin has the disadvantage of excessive cost and a recently recognized problem of permitting relapse. An assessment of our experience with 90 patients treated with orally given vancomycin showed there was good response in nearly all; however, in 19 percent diarrhea recurred with vancomycin-sensitive strains of *C difficile* after therapy was discontinued. The presumed mechanism for relapse is failure to eradicate *C difficile* due to sporulation. Other antimicrobials are attractive because of their more reasonable cost and in vitro activity against the pathogen. However, it is unlikely that they will obviate the problem of relapse, and none have established efficacy.

A final comment regarding management concerns epidemiologic aspects of the disease. Outbreaks of antibiotic-associated PMC have been observed in patients in hospital—a good example being the alarming incidence of *C difficile*-induced colitis on two wards of a hospital in Birmingham, England. *C difficile* in an individual case may come from the host's own colonic microflora, or it may be acquired from an extraneous source during antibiotic exposure. Clustering of cases suggests that the latter mechanism applies in some instances, and supports the concept that the pathogen is transferable. This emphasizes the importance of enteric precautions and care in keeping endoscopic instruments sterile.

The data summarized by George provide compelling evidence that *C difficile* is the major and possibly the exclusive cause of PMC. The detection of a microbial pathogen and subsequent therapeutic trials have justified the apparent paradox of antimicrobial treatment for an antibiotic complication. There remain nuances of the disease that pose problems to physicians, such as possible relapses, the cost of treatment and the logistics of having diagnostic tests carried out. Nevertheless, it appears that this dreaded iatrogenic complication is well on the way to being conquered.

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Will It Be Babble, Babel or Clarity of Language?

AN EDITOR of a professional journal of medicine feels compelled to comment when the subject "Babel in Medicine" is raised, as happens in a special communication appearing in this issue. This journal strives for literacy in the face of what often seem to be heavy odds. It tries to avoid ungrammatical constructs and professional jargon wherever possible, and to publish copy that is readily understandable to doctors of medicine and anyone else who reads and comprehends English.

English, when spoken and written correctly, is

a particularly expressive, precise and adaptable language. This may be one reason why it is now being used more and more for worldwide scientific and diplomatic communication. But perhaps just because it is so adaptable, it easily undergoes differentiation. There are many dialects, some geographical, some cultural and some related to professional disciplines or occupations such as medicine. But each differentiated dialect or subdivision of the language becomes fully understandable only to a specific segment of the population. Full communication with all who use the language is lost and Babel begins. In some settings further differentiation occurs. Code words develop with special and sometimes more or less secret meanings for those "in the know," which allows a system of communication to evolve within what appears on the surface to be ordinary use of the language or dialect. Moreover, differentation within the language can extend even to very small groups, such as the R-1, R-2, R-3, R-4 and R-5 in a teaching hospital, with the result that communication becomes only internal and much useful contact is lost with the outside world. The ultimate differentiation, the reduction to absurdity, is when no one but the speaker or writer can understand the noises that are made or the symbols that are written, at which point what might have been sensible communication will have turned into useless babble.

The Roman Catholic church provides an example of the value of a common language as a uniform means of communication over a wide range of situations. Ecclesiastical Latin has successfully spanned both the centuries and the continents, and has served well as an instrument to preserve the integrity and constancy of that institution. Medicine also needs a language for clear internal as well as external communication. It need not, and probably should not, be as rigid as ecclesiastical Latin—and it will not be if it is grammatical, well-constructed, clear and easily understood English. As physicians we owe genuine clarity of language to our patients, as well as to our colleagues and to the public.

—MSMW

CASE REPORTS

Refer to: Muther RS, Bennett WM: Peritoneal clearance of amphotericin B and 5-fluorocytosine. West J Med 133:157-160, Aug 1980

Peritoneal Clearance of Amphotericin B and 5-Fluorocytosine

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AMPHOTERICIN B AND 5-FLUOROCYTOSINE (5FC; also known as flucytosine) are the two most widely used and efficacious drugs for the treatment of systemic fungal infections. However, both pose unique problems to patients with renal disease. Although 5FC has no known renal toxicity, it is excreted in the urine and requires dosage modification in patients with renal insufficiency. Amphotericin B, on the other hand, has well-known dose-related renal toxicity. Because it has virtually no renal clearance, serum levels of amphotericin B are not significantly altered by the presence of renal disease. However, careful administration is necessary to avoid potential toxicity. Dosage schedules for both drugs in patients with renal insufficiency have been recommended.[1,2]

Despite the pronounced incidence of fungal infections in patients who are receiving long-term maintenance dialysis and have had renal transplants, surprisingly few data exist concerning the ability of amphotericin B and 5FC to be dialyzed. Two reports[1,3] show rather good plasma clearance of 5FC with hemodialysis but almost no clearance of amphotericin B. Less information exists regarding the clearance of either drug by peritoneal dialysis, however. Therefore, we have evaluated peritoneal dialysate levels of both amphotericin B and 5FC in a patient with cryptococcal sepsis.

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Submitted, revised, November 5, 1979.

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Report of a Case

In a 48-year-old man with end-stage renal disease maintenance hemodialysis was begun in December 1977. In August 1978, the patient had a successful renal transplant. Following an episode of acute rejection, serum creatinine levels stabilized at 2 mg per dl, and he was given maintenance doses of imuran and prednisone. In October 1978 the patient was admitted to hospital and treated for a second acute allograft rejection with 350 mg of prednisone per day for five days. Although there was some initial improvement in renal function, levels of serum creatinine slowly but progressively rose, and peritoneal dialysis was begun. During the third week of his hospital stay, the patient became febrile, confused and lethargic. An x-ray study of the chest showed an infiltrate of the right lower lobe. All bacterial cultures were negative but fungal cultures from the sputum, blood and cerebrospinal fluid (CSF) grew *Cryptococcus neoformans*. The peritoneal fluid was unremarkable. Imuran was discontinued and administration of amphotericin B was increased to a maintenance dose of 30 mg per day. The patient was also given 750 mg of 5FC orally every six hours. There was a good clinical response to this regimen, with resolution of fever and improvement in sensorium. Repeat analysis of spinal fluid failed to show a cryptococcal infection. Amphotericin B was continued until the patient received a total dose of 1.3 grams. Administration of 5FC was continued for five weeks. The minimum inhibitory concentration (MIC) of 5FC for the infecting strain of *Cryptococcus neoformans* was 2.2 μg per ml. The MIC was 0.2 μg per ml for amphotericin B.

Materials and Results

Amphotericin B and 5FC were measured in the serum and peritoneal dialysate on several occasions. On one day both peak and trough levels of 5FC (in relation to the administered dose) were measured. Dialysis was carried out over 36 hours (30 passes of 1,500 ml per pass). Results are shown in the graphs in Figures 1 and 2.

The measurement of 5FC in the serum and dialysate was made by the agar-diffusion method. A reference strain of *Candida albicans* with known resistance to amphotericin B was added to a yeast

nitrogen base (YNB) agar (Prepared Media Lab, Portland, OR) and the medium poured onto plates. Disks containing the patient's serum, dialysate and standard concentrations of 5FC were placed on the agar surface and zones of inhibition were measured. A standard reference curve was drawn, plotting the results on semilogarithmic paper. Levels of 5-fluorocytosine were determined by correlating zones of inhibition to the standard reference curve.

Amphotericin B was measured by the broth dilution method. Twofold tube dilutions of the patient's serum and dialysate were made with trypticase soy broth. A standard inoculum of *Candida albicans* (10^5 organisms per ml) resistant to 5FC was then added to each tube. Levels of the antibiotic were calculated by multiplying the MIC by the degree of dilution-inhibiting growth.

Levels of 5FC in the peritoneal dialysate were significant and averaged 65 percent of the serum levels during dialysis. After seven days without dialysis the serum and peritoneal fluid levels of the drug were identical (probably reflecting prolonged equilibrium time). Intraperitoneal levels of amphotericin B were low and were not detected consistently by our assay despite high serum levels. Results are displayed graphically in Figures 1 and 2.

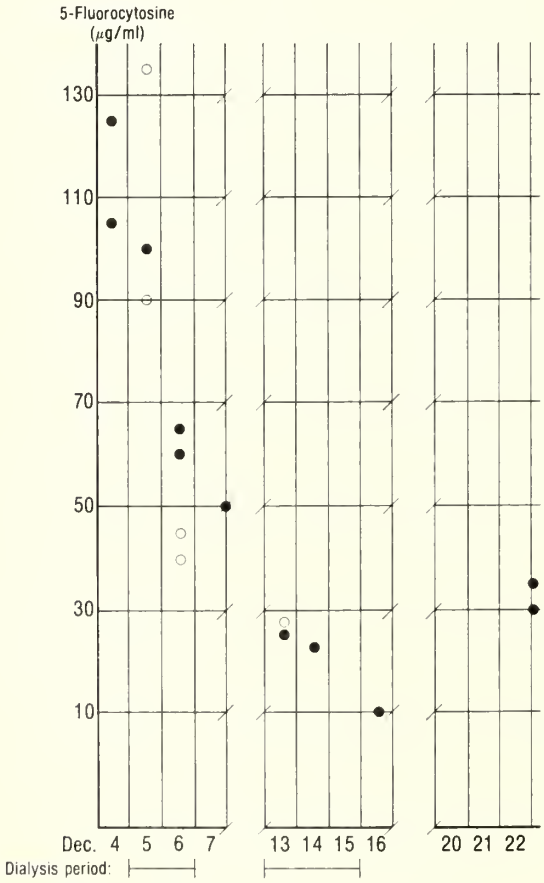

Figure 1.—Serum (closed circles) and dialysate (open circles) levels of 5-fluorocytosine using the agar assay. Points on the same day represent peak and trough levels.

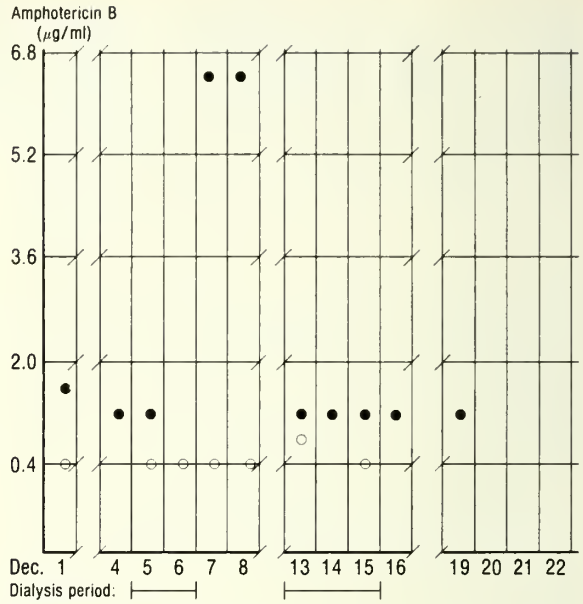

Figure 2.—Serum (closed circles) and dialysate (open circles) levels of amphotericin B using the broth dilution assay. Dosage of amphotericin B was 30 mg per day.

Peritoneal clearance of 5FC was calculated using the following formula:

$$C_{5FC} = CD \times QD/C_P.$$

CD is the mean out-flow dialysate concentration, C_P the mean serum concentration over the dialysis period, and QD the mean dialysate flow rate over the 48-hour dialysis period in ml per minute. Using this formula, the peritoneal clearance of 5FC was calculated to be 14 ml per minute.

Discussion

Amphotericin B and 5-fluorocytosine pose unique problems in the management of patients with renal disease and fungal infection. Until recently, relatively little was known about whether either of these drugs could be removed by dialysis, particularly by peritoneal dialysis. In animals, Koechlin and colleagues[4] showed urinary excretion of 5FC after the drug was administered intraperitoneally. Two case reports show similar absorption after intraperitoneal administration of 5FC in humans.[5,6] Drouhet and co-workers[3] pro-

vided the only previous evidence of 5FC in the peritoneal dialysate of three patients who had been given the drug orally. Except for one patient with peritonitis, however, peritoneal levels of the drug averaged only 5 percent of serum levels. Our results suggest good clearance of 5FC by peritoneal dialysis, and show intraperitoneal levels of 5FC of between 60 percent and 100 percent of serum levels of the drug.

Previous data[1] have shown that amphotericin B is poorly dialyzed from the blood, but no previous information has been recorded regarding its peritoneal clearance. Intraperitoneal levels of amphotericin B were virtually undetectable in our patient despite substantial levels found in the serum. Thus, we conclude that there is no significant peritoneal clearance of amphotericin B by peritoneal dialysis.

Peritoneal clearance is dependent on a variety of factors including molecular size, percent of protein-binding and water solubility. Generally, drugs which are normally excreted by glomerular filtration are cleared well by peritoneal dialysis. Examination of the pharmacokinetics of amphotericin B and 5FC provides evidence to explain the pronounced difference in their peritoneal clearance. Amphotericin B is highly protein-bound (more than 90 percent), and when bound in the serum it circulates in a complex of high molecular weight (200,000-300,000).[1] There is minimal penetration of CSF, parotid glands and aqueous humor.[1] One would therefore not expect significant peritoneal permeability of the drug and, indeed, we could document none.

The drug 5FC, on the other hand, is poorly protein-bound ($<$ 5 percent).[5,7] A molecular weight of 129 allows free filtration by the renal glomerulus and 90 percent is recovered unchanged in the urine after an intravenous or oral dose.[7] Penetration of CSF and aqueous humor is good.[4]

By using the peritoneal clearance formula ($C_{5FC} = CD \times QD/C_P$), we calculate a 5FC clearance of 14 ml per minute. Although this formula does not correct for ultrafiltration, decreasing plasma concentrations with time and clearance occurring during the in-flow and out-flow of dialysis, it does express the average amount of plasma cleared per minute. The clearance of 14 ml per minute approximates the peritoneal clearance of creatinine (13 ml per minute) and urea (18 ml per minute) (according to telephone conversation in February 1979 with Karl Nolph, MD, Professor of Medicine, University of Missouri Medical Center). This should not be surprising considering that the molecular weight, degree of protein-binding and renal handling of 5FC are virtually identical to that of creatinine.

The relative peritoneal permeability of 5FC and amphotericin B may have important clinical implications. Because of significant peritoneal clearance of 5FC, the administered dose may need further adjustment in patients receiving peritoneal dialysis. Without an increase in dose, serum levels may fall below the therapeutic range during dialysis periods.

There may also be significant therapeutic implications in patients with fungal peritonitis. Previous reports[8-10] imply the efficacy of parenterally given amphotericin B in treatment of *Candida albicans* peritonitis. In two of the cases reported, however, the removal of Tenckhoff peritoneal catheters and discontinuation of broad-spectrum antibiotics may have aided resolution of the infection. Intraperitoneally given amphotericin B has been used to treat fungal peritonitis,[10,11] although peritoneal irritation limits its practicality. Both oral[3] and intraperitoneal[5,6,12] administration of 5FC have been used to treat fungal peritonitis with good clinical results. In one of these cases, Holdsworth[6] showed a peritoneal clearance of 5FC which was 30 percent that of creatinine. Thus, one might theorize that 5FC could be more efficacious than amphotericin B in the treatment of fungal peritonitis. However, evaluation of its concentration in peritoneal tissue as well as its ability to be dialyzed across an inflamed peritoneum would be required before such an interpretation is justified.

Our data suggest insignificant peritoneal clearance of amphotericin B, whereas the clearance of 5FC by peritoneal dialysis appears to be excellent. However, the theoretical advantage of 5FC in the treatment of fungal peritonitis needs further documentation.

Summary

Peritoneal clearance rates of amphotericin B and 5-fluorocytosine were evaluated in a patient with cryptococcal sepsis who was receiving peritoneal dialysis. The peritoneal clearance of 5FC was 14 ml per minute, approximating peritoneal clearance of urea and creatinine. Amphotericin B could not be detected in the peritoneal fluid. These findings may have potential therapeutic implications in the treatment of fungal peritonitis.

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Refer to: Connors MH: Growth and maturation arrest, hypochromic anemia and hyperglobulinemia associated with a brain tumor. West J Med 133:160-163, Aug 1980

Growth and Maturation Arrest, Hypochromic Anemia and Hyperglobulinemia Associated With a Brain Tumor

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ARREST OF GROWTH and sexual maturation by brain tumors that increase intracranial pressure may be associated with hypothalamic-pituitary suppression.[1] This latter mechanism appeared relatively unimportant in the case of a teenage boy with short stature, sexual immaturity, refractory hypochromic anemia, hyperglobulinemia, hepatosplenomegaly and a brain tumor. Previously, the syndrome of a refractory form of hypochronic anemia, hypergammaglobulinemia and growth arrest had been reported associated with abdominal hamartomatous lymphoid tumors.[2] The finding of increased levels of growth hormone in the serum provides further information on this refractory clinical condition.

Report of a Case

The patient, a 15½-year-old boy, was referred to us because of arrest of growth, lack of sexual maturation and continued anemia despite iron therapy. From the age of 12½ years the boy's parents had noted a decrease in the rate of his growth; however, they did not seek treatment for this condition. The boy noted that during the first years of school he had been one of the biggest children in his class. Later, however, he was brought to his pediatrician because of the teasing he received over his small size. He was found to be anemic. Following a month of iron therapy (45 mg per day) with failure to respond, further evaluation of the boy's condition was requested. His father was 190.5 cm (6 foot 3 inches) and his mother 167.6 cm (5 foot 6 inches) tall. A 13-year-old brother was 10.2 cm (4 inches) taller than the patient.

The patient's only other complaint was frontal headaches every few months that would last a couple of days. There was no associated vomiting. He was otherwise active and doing well in school.

On physical examination the boy was found to be pleasant and freckle-faced. Head circumference was 56 cm (mean for that age), height 147.5 cm (4 feet 8 inches) and weight 37 kg (81.6 pounds) —both less than the 5th percentile and mean for 11½ years. The skeletal age was 10 years. Blood pressure was within normal limits. Funduscopic examination showed bilateral papilledema and tortuous veins. A defect in the right superior quadrant was found on visual field testing. The liver was palpated 4.5 cm below the right costal margin and the spleen was enlarged 2.5 cm below the left costal margin. Both were smooth and not tender. The testes were descended and measured 1.6 cm in their longest diameter. The penis was 7.5 cm in length. No pubic or axillary hair was present. No abnormalities were found on neurological testing.

Studies of the blood (Table 1) gave the following values: hemoglobin 8.0 grams per dl, with 1.0 percent reticulocytes and a corrected sedimentation rate of 140 mm per hour. Erythrocyte

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TABLE 1.—*Laboratory Data Before and After Treatment of Brain Tumor*

Time	Hemoglobin (grams/dl)	Hematocrit (percent)	Iron-Binding Capacity (μg/dl)	Serum Protein			Immunoglobulins		
				Total (grams/dl)	Albumin (grams/dl)	Globulin (grams/dl)	Gamma G (mg/dl)	Gamma A (mg/dl)	Gamma M (mg/dl)
Preoperation	8.0	26.2	266	9.2	2.9	6.3	2,690	1,050	200
Postoperation									
16 days	11.3	34.3	236	7.5	3.2	4.3	..	..	..
6 months	10.3	31.1	254	7.8	3.5	4.3	1,660	1,220	170
12 months	9.3	29.2	..	6.8	3.4	3.4	..	..	..

count showed a mean corpuscular volume of 55 μ^3, mean corpuscular hemoglobin of 17.1 $\mu\mu$g and mean corpuscular hemoglobin concentration of 30.7 percent. The bone marrow had 50 percent cellularity with a myeloid-erythroid ratio of 1:1. Maturation of all cell lines was normal. Plasma cells made up 5 percent to 10 percent of the nucleated cells. On staining, no iron was seen. The level of iron in the serum was low (38μg per dl) as was the total iron-binding capacity (266 μg per dl).

Blood chemistry measurements for electrolytes, glucose, urea nitrogen, creatinine, uric acid, bilirubin, calcium, inorganic phosphate and cholesterol were within normal range. However, the level of alkaline phosphatase in the serum was elevated: 384 mU per ml heat stabile and 216 mU per ml heat labile (normal for age, 400 mU per ml total, with heat stabile less than 25 percent). Liver enzyme levels were normal. Partial thromboplastin time was 41.6 seconds with a control time of 33 seconds. Prothrombin time was 14.4 seconds with an 11-second control time. The quantitative fibrinogen concentration was elevated at 1,100 mg per dl and no fibrin split products were noted.

Analysis of urine showed an osmolality of 703 mOsm with proteinuria (2+). Electrophoresis of this protein showed 16.8 mg per dl of albumin; the globulins measured: alpha-1 11.8, alpha-2 30.4, beta 22.4 and gamma 18.6 mg per dl.

Radiographic studies included normal skull and sella turcica findings. On admission a computerized axial tomographic (CAT) scan was carried out. The findings were interpreted as normal. However, a repeat scan with contrast material showed a large enhancing homogeneous mass along the left margin of the tentorium. Cerebral angiography defined the mass above and below the tentorium on the left side.

Endocrine evaluation indicated normal thyroid function with serum thyroxin at 9.6 μg per dl and thyroid-stimulating hormone levels within normal limits. Insulin tolerance testing was carried out using regular insulin (0.1 unit per kg of body weight, given intravenously as a bolus). The fasting serum glucose concentration decreased from 88 to 53 mg per dl at 30 minutes and returned to 76 mg per dl at 60 minutes. Concentration of human growth hormone was elevated to between 12 and 15 ng per ml resting and rose to 23 ng per ml at 30 minutes. There was no increase in the concentration of serum cortisol (11 μg per dl) following the decrease in concentration of serum glucose. Analysis of a 24-hour specimen of urinary steroid metabolites showed normal levels of 17-ketosteroids (6 mg) and 17-ketogenic steroids (10 mg) for his size.

In preparation for the surgical operation, the patient was given fresh frozen plasma to correct defects in coagulation. Cold agglutinins and difficulty in cross matching for blood transfusion were noted. During the operation the tumor was detected immediately upon elevation of the occipital lobe. The tumor bled freely and several hours were required to carefully remove tumor tissue from above and below the tentorium. Because of its attachment near the straight sinus, the tumor was trimmed as much as was felt safe; approximately 85 percent of the tumor mass was removed. The type of the tumor could not be identified from frozen sections. Following permanent fixation of the tumor tissue the histologic diagnosis has remained controversial. One neuropathologist found the tissue specimen suggestive of a chordoma while consultants from the Armed Forces Institute of Pathology suggested that the tissue represented an unusual variant of an angioblastic meningioma of the hemoangioblastic type. During the patient's recovery, there was a decrease in the size of the liver and spleen and hematologic studies showed improvement.

Six months following the surgical operation, the patient had five weeks of radiotherapy, with a total dose of 5,000 rads administered to the posterior fossa. At that time, the boy's height had increased 3.8 cm (1.5 inches) (Figure 1). No disturbances of vision were noted. Evidence of

sexual maturation included larger testes (3 cm bilaterally) and pubic hair.

Measurement of serum growth hormone was 2.0 ng per ml at rest, and serum gonadotropin and testosterone levels were appropriate for the stage of puberty. A CAT scan showed no change in the residual tumor. Hematologic findings were slightly worse (Table 1); however, there was no enlargement of the liver or spleen.

A year following the operation, the patient's growth and pubertal maturation had progressed further (Figure 1). At that time, the level of resting serum growth hormone, 1.2 ng per ml, was within normal limits.

Discussion

The association of hypochromic anemia, hypergammaglobulinemia and arrest of growth has been reported by Neerhout and co-workers[2] in association with a mesenteric lymphoid hamartoma. In their review of the literature, they found two other cases with similar characteristics, with the exception of growth failure in one, and associated with mediastinal or abdominal lymphoid masses. There was reversal of symptoms with removal of the tumor. Although the identification of the tumor type in our patient has been controversial, it in no way resembles the lymphoid hamartomas described in these cases. Also, the tumor under discussion here had no relationship to the pineal body. Cell mitoses were rarely seen and the tumor was apparently not frankly malignant.

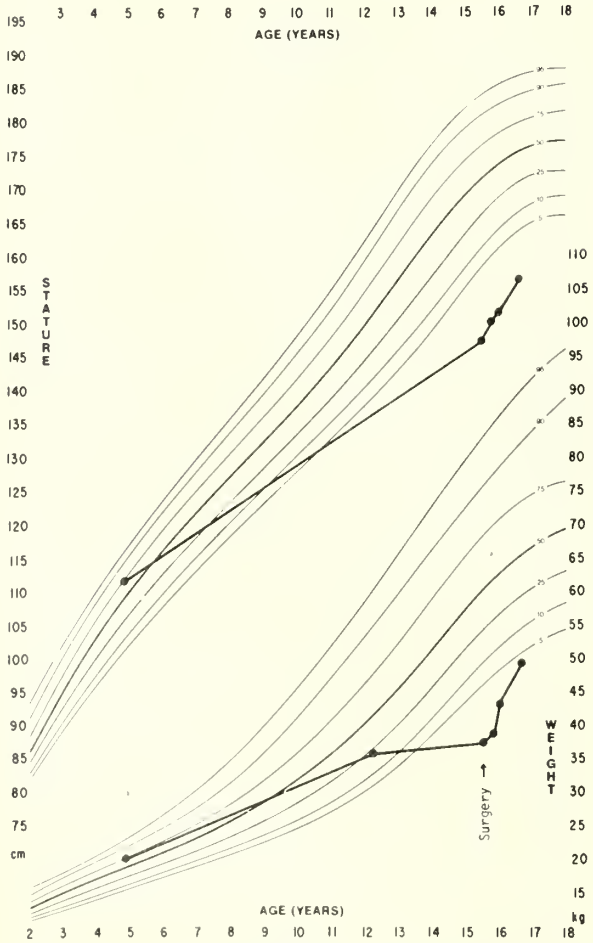

Figure 1.—Above average size is shown for the patient at 4 years 9 months of age, as well as accelerated pattern of growth following removal of tumor.

Despite the difference in location and pathological aspects of the tumor, the clinical features were quite similar to those previously reported. The low levels of serum iron, low iron-binding capacity and refractoriness to iron therapy present in all of the cases remains unexplained. Whether the persistent proteinuria results in transferrin deficiency cannot be answered. In our patient these features did not improve with partial removal and irradiation of the remaining tumor tissue. Splenomegaly and hepatomegaly resolved after the operation despite continued elevated levels of gamma globulins.

Intact pituitary function was supported by the findings of normal thyroid and adrenal function. The failure of the cortisol level to rise in the presence of hypoglycemia may result from the inadequacy of the stress. The prompt return to a normal serum glucose concentration following this test is supportive of intact pituitary-adrenal function as are the normal concentrations of adrenal metabolites in the 24-hour urinary specimen. Cortisol insufficiency by itself may be associated with increased linear growth.[3] The finding of increased levels of growth hormone at rest may indicate a refractory state to growth hormone. Occasionally in a child, there may be elevated levels of growth hormone at rest because of anxiety. The two baseline determinations of growth hormone, done 30 minutes apart, were both elevated in our patient, and the resting cortisol level did not reflect any unusual stress. Similar resting growth hormone elevations have been reported in cases of severe protein calorie malnutrition such as kwashiorkor.[4] In this condition, increased levels of growth hormone are associated with a low to absent concentration of somatomedin. With protein repletion there is a reversal of symptoms. The genetic form of growth

hormone resistance is found in the case of Laron dwarfism, where growth hormone levels are elevated while somatomedin concentrations are low.[5] It has been suggested that growth hormone may influence erythropoietin[6]; however, this effect is not a pronounced one, nor is it clinically apparent in children with isolated growth hormone deficiency or Laron dwarfism. Unfortunately, measurements of somatomedin were not done in this study to support this possibility.

The catch-up growth that occurred in our patient was associated with a return to normal levels of measurable growth hormone and the onset of puberty. It is, therefore, difficult to separate these influences on the acceleration of the boy's growth, and it is likely that both were needed.[7] The possibility that release of gonadotropin occurred as the result of the brain operation, thereby stimulating puberty is also a consideration. Other authors[8] have reported pituitary insufficiency following radiation therapy to the brain that excludes the pituitary gland.

The accelerated growth seen in patients after removal of lymphoid hamartomas favors a systemic influence. However, no hormonal measurements are available in these studies. Because of the clinical similarity in our patient's course following the operation, a similar mechanism is favored.

Summary

A brain tumor developed in a 15½-year-old boy with associated arrest of growth (despite the presence of growth hormone) and of sexual maturation, refractory hypochromic anemia and hyperglobulinemia. A similar clinical triad has been reported with lymphoid hamartomas, although the tumor did not resemble this type of tissue growth. After partial removal of the tumor, catch-up growth and sexual maturation occurred with minimal improvement in the anemia. These observations indicate that certain tumors through associated immunological mechanisms have an etiologic role in this clinical pattern.

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Furosemide and Ethacrynic Acid in Acute Tubular Necrosis

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OLIGURIC ACUTE RENAL FAILURE (ARF) is a syndrome characterized by a rapid decrease in renal function with progressive azotemia and oliguria (urine output of 50 to 400 ml per 24 hours).[1] Major causes of this syndrome are prerenal azotemia (such as volume depletion), postrenal obstruction (such as prostatic hypertrophy), renovascular disease (such as renal artery emboli) and parenchymal renal disease (such as glomerulitis or acute tubular necrosis).[1,2] By far the most common cause of ARF is acute tubular necrosis (ATN), which represents about 75 percent of all cases.[1]

Mannitol has been recommended for both diagnosing and treating ARF, although considerably more is known about the use of the loop diuretics furosemide and ethacrynic acid in this syndrome. It has been proposed that a successful diuresis in response to large intravenous boluses of these latter drugs helps differentiate prerenal azotemia from ATN.[3] Others have suggested that furosemide and ethacrynic acid are effective in

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ABBREVIATIONS USED IN TEXT

ARF = acute renal failure
ATN = acute tubular necrosis
GFR = glomerular filtration rate

the treatment of acute tubular necrosis.[4-17] However, serious adverse effects, including permanent deafness, have been attributed to both agents.[18-31] Until now, a thorough discussion of the risks and benefits of using the loop diuretics in the treatment of ATN has not been attempted.

Over the past two years, the Division of Clinical Pharmacology has evaluated two patients with almost identical histories, one of whom is presented below. Both patients became deaf suddenly during diuretic treatment of ATN. Such cases focus physicians' attention on an important question: Do the potential risks of these drugs outweigh their potential benefits in patients with ATN? After examining existing evidence, one can formulate tentative conclusions guiding therapy for similar patients.

Report of a Case

Septic shock developed five days after an uncomplicated cesarean section in a 25-year-old woman. The 60-kg (132-pound) woman previously had been well. Therapy was begun with clindamycin (300 mg given intravenously every 6 hours) and gentamicin (60 mg given intravenously every 12 hours). Despite administration of fluids intravenously, which restored pulmonary capillary wedge pressure to normal, oliguria developed over the next 12 hours. Administration of gentamicin was discontinued after the second dose; dopamine was given without benefit. Acute tubular necrosis was diagnosed by the medical history, analysis of the urine (many darkly pigmented granular casts) and a renal failure index greater than 5. Two rapid intravenous pushes of furosemide, 120 mg followed by 360 mg several hours later, were given in an unsuccessful attempt to increase urine output. Finally, 150 mg of ethacrynic acid was administered in an intravenous push. Minutes later the patient noted the sudden onset of bilateral deafness, and could hear only shouted commands. There were no vestibular symptoms or signs. Over the next few days, her condition stabilized; sepsis (*Staphylococcus epidermidis* was cultured from blood) responded to oxacillin, and her azotemia resolved completely. She was discharged home with permanent bilateral sensorineural deafness documented by audiometry.

Cause of Deafness

The sudden onset of deafness in this case strongly suggests that it was induced by one or more of the three potentially ototoxic medications that the patient received. The first was gentamicin, given in two intravenous doses of 60 mg, each representing 1 mg per kg of body weight. Gentamicin ototoxicity has been well described, occurring in about 2 percent of treatment courses.[32] Vestibular toxicity is more common; however, hearing problems also occur, usually as a gradual hearing loss involving high-range frequencies. Because of the sudden development of deafness, including speech frequency, more than 12 hours after a very modest dose of gentamicin, it is unlikely that this drug is primarily responsible for this defect.

The patient then received furosemide, in two large, rapid intravenous pushes. Furosemide-induced deafness is an uncommon adverse effect, which has been noted in large drug surveillance studies, occurring in less than 0.2 percent of patients receiving "usual" doses (less than 80 mg) for congestive heart failure or edema.[33-35] However, there are now at least eight reported cases of temporary losses of hearing[18,29-31] and six of permanent deafness,[21,27] probably caused by furosemide. Deafness induced by this drug usually occurs suddenly, minutes after a rapid intravenous bolus of more than 100 mg, although doses as low as 60 mg have caused transient deafness.

In every case reported, there was some degree of underlying renal failure, usually ARF. However, intravenously given doses greater than 100 mg are rarely administered for conditions other than acute renal failure. Hearing losses were characterized by increased pure-tone sensorineural hearing thresholds, maximal in the middle range of frequencies.[27,36] The mechanism of furosemide-induced deafness is unknown. Although the half-life of furosemide is increased in patients with renal failure,[37] this would not explain the rapid onset of ototoxicity.

It appears that loss of hearing is related to the rate of administration of furosemide. In a study of 16 uremic patients, Wigand showed that infusion of 1,000 mg of furosemide at 25 mg per minute produced acute reversible hearing loss (documented with both pure-tone and speech

audiograms) in half the subjects, maximal in the middle range of frequencies.[36] A second study with azotemic patients showed that furosemide administered at 25 mg per minute produced "noticeable hearing loss" in 60 percent of the subjects, while infusion at 15 mg per minute produced only "minor hearing losses which the subjects were not aware of."[38]

The third potentially ototoxic drug that the patient received was ethacrynic acid, given just minutes before she suddenly became deaf. Since the first report of ethacrynic acid-induced deafness in 1965,[22] there have been at least 15 reported cases of transient deafness and 11 cases of permanent deafness.[18-20,23-26,28] Administration of ethacrynic acid in "usual" doses (less than 100 mg) to patients in hospital with heart failure or edema resulted in deafness in less than 0.7 percent of treatment courses.[39] Deafness induced by ethacrynic acid usually develops within 15 minutes of a rapid intravenous injection, and has been observed following doses as small as 50 mg.

The mechanism of ethacrynic acid-induced deafness is unclear. Bilateral loss of outer hair cells was noted in one patient at autopsy.[40] A recent study showed that ethacrynic acid caused a large and rapid change in endolymph electrolyte concentrations in dogs.[41] In only ten minutes, ethacrynic acid caused the potassium concentration to decrease from 145 to 21 mEq per liter, while the sodium concentration rose from 5.9 to 143 mEq per liter. The fact that this shift was rapid, large and persistent, and did not occur in the perilymph, suggests that this might be the mechanism for ethacrynic acid-induced deafness.

In summary, this patient's sudden deafness seems to have been caused by a rapid injection of 150 mg of ethacrynic acid. Whether the previous doses of furosemide or gentamicin produced additive or synergistic ototoxicity, an occurrence implied by some authors but never proved, remains an open question.

Other than deafness, the risks of these two diuretics are not great. The most common problems—fluid and electrolyte abnormalities—are seen in 5 percent to 25 percent of patients in hospital who receive conventional doses of the drugs.[33-35,38,42] These adverse effects are reversible, and probably occur less often in oliguric patients who are closely monitored. Other side effects such as nausea, vomiting and epigastric pain occur in less than 10 percent of patients, and are usually transient.[29,33-35,38] Rashes, agranulocytosis and necrotizing pancreatitis have been reported, but seem to occur only rarely.[43,44]

Use of Loop Diuretics

Loop diuretics might benefit a patient with acute tubular necrosis in several ways.[1,45,46] First, by decreasing the reabsorption of filtrate in the tubules and increasing intratubular pressure, they might minimize the obstruction of tubules by cell debris and precipitated pigment or proteins. Second, their direct vasodilator effect might reverse the arteriolar vasoconstriction and decreased renal blood flow seen in the early stages of ATN. It is unknown whether tubular leakage of filtrate or decreased glomerular permeability, also found in ATN, are modified by these agents.

Third, it is difficult to ascribe a cause-and-effect relationship between the administration of a diuretic and subsequent diuresis. Muth[47] described almost identical clinical courses in two patients with ATN. In both patients a sudden brisk, sustained diuresis occurred, which was associated with increased glomerular filtration rate (GFR). However, in one patient, diuresis occurred several hours after the patient was given furosemide; in the other patient, diuresis occurred without diuretics. How can one prove that the first patient's diuresis was produced by furosemide?

After reviewing all the potential problems raised in studies dealing with such a varied syndrome as oliguric ATN, one can understand Muth's conclusion: "The task of discussing the prevention or treatment of this unpredictable, usually self-limited, sometimes unrecognized syndrome of various and often unknown etiologies may be as perplexing as the problem itself."[47]

In Diagnosing ATN

In patients in whom other causes of ARF have been ruled out, it is necessary to distinguish prerenal azotemia from acute tubular necrosis. Merrill[3] proposed that a positive response to the loop diuretics distinguished the two syndromes. However, there are no data available which show the sensitivity of this "diuretic challenge test" (the percentage of patients with prerenal azotemia in whom diuresis occurs), or its specificity (the percentage of patients with ATN in whom diuresis does not occur).

Others have emphasized the importance of laboratory tests in this regard. The first urinary sediment study is diagnostic of ATN in 80 percent of patients, showing many darkly pigmented,

TABLE 1.—*Use of Furosemide in Patients With Acute Renal Failure in Four Controlled Studies*

*Reference and No. of Patients**	*Assignment (comparison)†*	*Proof of Oliguric ATN (duration)*	*Furosemide*		*Adverse Reactions*	*Duration of Oliguria (days)*	*Duration of Azotemia*	*Dialysis Requirement*	*Time to a Diuresis of >1,500 ml/day*	*Mortality*
			Dose	*Rate*						
Beroniade[13] C=12 T=12	Not random (similar cause)	Inadequate (3-6 days)	60-480 mg every day	?	Numbness (1)	10.6 *vs* 14.5 (NTFS)‡	?	8 *vs* 12 patients (NTFS) [P>0.2]§	?	3 *vs* 6 patients (NTFS) [P>0.2]§
Cantarovich[14,15] C=13 T_1=19 T_2=15	Not random (similar cause, duration)	Inadequate (average 2 days)	600 mg every day (fixed dose) 100-3,200 mg every day (progressive dose)	5 mg/min 5 mg/min	Tinnitus if rate >14 mg/min	NSD¶ 5.7 *vs* 15.0 (P<0.02)	NSD NSD	NSD 2.8 *vs* 8.8 sessions (P<0.02)	NSD 9.7 *vs* 21.8 days (P<0.005)	NSD NSD
Cantarovich[15] C=19 T=39	Not random (similar duration)	Adequate (average 2 days)	2,000 mg every day	4 mg/min	0	7.0 *vs* 14.0 (P<0.005)	NSD	4.9 *vs* 9.6 sessions (P<0.05)	10.0 *vs* 19.6 days (P<0.02)	NSD
Kleinknecht[50] C=33 T=33	Random (similar cause, duration, severity)	Adequate (variable)	1.5-6 mg/kg of body weight every 4 hours	Over a few minutes	Transient tinnitus, deafness (several patients)	NSD	NSD	NSD	4.0 *vs* 8.3 days (P<0.01)	NSD

ATN=acute tubular necrosis; NSD=no significant difference; NTFS=not tested for significance

*Number of patients in treatment (T) and control (C) groups
†Method of patient assignment to treatment and control groups, and comparison between groups.
‡Not tested for significance by author.
§P value by one-tailed Fisher exact test.
¶No significant difference at α=0.05 level.

granular casts.[1] Miller and co-workers[48] have recently shown the sensitivity (90 percent) and specificity (96 percent) of two urinary indices, the renal failure index (RFI) and the excreted fraction of filtered sodium (FE_{Na}) study, in diagnosing acute tubular necrosis. The equations for the two indices are as follows:

$$RFI = \frac{U_{Na}}{U/P_{Cr}} \text{ and } FE_{Na} = \frac{U/P_{Na}}{U/P_{Cr}} \times 100$$

U_{Na} = urine sodium
U/P_{Cr} = urine/plasma creatinine
U/P_{Na} = urine/plasma sodium

Because these noninvasive tests have proven sensitivities and specificities, and no associated morbidity, the diuretic challenge test is not indicated when attempting to differentiate prerenal azotemia from acute tubular necrosis.[1,49]

In Treating ATN

The recent literature includes numerous reports concerning the therapeutic use of loop diuretics in patients with acute renal failure. Among these are 4 controlled studies (Table 1)[13-15,50] and 13 uncontrolled series of patients (Table 2).[4-12,16,47,51] The number of patients in each of the 17 studies ranged from 2 to 49. Causes of ARF other than ATN were excluded in only ten of the studies. Duration of renal failure before beginning treatment varied from several hours[8,47] to many days,[6,51] and size of dose, frequency and rate of administration also varied widely. All doses were given intravenously except in Epstein's study, where furosemide was infused directly into the renal artery.[51]

No author ascertained ototoxicity using audiometry; all relied on patient complaints or routine physical examinations. Even so, five authors reported transient or permanent deafness in some of their patients. And in one patient, spontaneous atrial fibrillation developed while the patient was receiving a bolus of furosemide through a central venous line.[17]

The 13 uncontrolled series attempted to answer one important question: Does the use of a loop diuretic produce a sustained diuresis in patients with ATN? Of the 275 patients, a sustained diuresis of greater than 1,000 ml per 24 hours was reported in 120 (44 percent).

However, there are serious difficulties in interpreting these data. First, seven of the studies either failed to show that all patients had ATN, or admittedly included patients with ARF resulting

from other causes (see Table 2). And in two of the studies, it is not stated whether the diuresis was sustained. The time between administration of the diuretic and subsequent diuresis was not described in three studies, and in a fourth it was as long as 96 hours. More important, in no study could it be proved that an observed diuresis occurred as a direct result of administration of the drug.

It is also important to know whether diuresis is accompanied by a fall in the serum creatinine level, indicating an increase in glomerular filtration rate (GFR). Six series did not include data on this point. In the seven which did, sustained diuresis was associated with a fall in creatinine levels in fewer than half the cases. In the one controlled study that considered this question, sustained diuresis "early" in the course of ATN was noted in 3 of 33 treatment patients in 2 of 33 control patients.[50] Finally, an associated increase in GFR was noted in only two of these five patients.

The four controlled studies examined differences between control and treatment groups with respect to five major factors: duration of oliguria, duration of azotemia, dialysis requirements, time to onset of a diuresis greater than 1,500 ml per day and mortality. However, several problems in these studies should be mentioned. Patient assignment was random in only one study.[50] Beroniade[13] matched control patients to treatment patients with ARF of similar cause and duration. Patient assignment in Cantarovich's two studies[14,15] is unclear, although random assignment was not used. Also, ATN as the cause of acute renal failure was not sufficiently shown in two of the studies.[13,14]

TABLE 2.—*Use of Diuretics in Patients With Acute Renal Failure in 13 Uncontrolled Series*

Reference	*No. of Patients*	*Proof of Oliguric ATN (duration)**	*Drug*			*Adverse Effects*	*Induction of Sustained Diuresis (onset)‡*	*Associated Decrease in Creatinine*
			Name	*Dose†*	*Rate*			
Auger[4]	2	Adequate (1-5 days)	EA M	50 mg×1 or 2 25 mg×1 or 2	over 15 min	0	2/2 (<4 hours)	?
Castro[5]	14	Adequate (>24 hours)	FR	500 mg×1	4 mg/min	?	5/14 (<24 hours)	?
Desmonts[6]	8	Adequate (1-14 days)	FR	20 mg every hour	?	0	8/8 (12-96 hours)	?
Fries[7]	22	Inadequate (?)	FR	500-1,000 mg every day	3 mg/min	0	13/22 (<24 hours) [?sustained]	?
Sullivan[8]	3	Inadequate (12-24 hours)	FR	80-2,000 mg every 4 hours	?	0	2/3 (<24 hours)	?
Olmer[9]	24	Inadequate (?)	FR	100 mg every 4 hours	?	0	11/24 (<24 hours) [?sustained]	?
Humbert[10]	22	Inadequate (?)	FR	125 mg every 3 hours	?	0	14/22 (<6 hours)	no
Kjellstrand[11]	13	Inadequate (3-216 hours)	EA M	1 mg/kg of body weight×1 variable	over several min	t. deafness (1) p. deafness (1)	4/13 (<4 hours)	no
Beaufils[12]	41	Adequate (?)	FR	160 mg every 6 hours	?	t. deafness (1)	27/41 (<3 hours)	yes in 11/27
Brown[16]	49	Adequate (?)	FR	250-1,000 mg×1	<33 mg/min	?	11/49 (?)	yes in 4/11
Stott[17]	29	Adequate (?)	FR	250-500 mg×1	<50 mg/min	A. fib. (1) tinnitus (most)	5/29 (?)	yes in 3/5
Muth[47]	42	Inadequate (<24 hours)	FR	100-1,000 mg every 3 hours	<16 mg/min	0	17/42 (?)	yes in 7/17
Epstein[51]	6	Adequate (2-9 days)	FR	280 mg×1 [intra-arterial]	10 mg/min	?	1/6 (3 days)	yes in 1/1

A. fib. = atrial fibrillation; ATN = acute tubular necrosis; EA = ethacrynic acid; FR = furosemide; M = mannitol; p. = permanent; t. = temporary

*Duration of oliguria at time diuretics were begun.
†Dose size and frequency.
‡Time of onset of sustained diuresis after first dose of diuretic.

Despite these problems, these studies provide the best data available at present.

Duration of oliguria. Beroniade[13] found that patients in the treatment group had a shorter average duration of oliguria than those in the control group (10.6 versus 14.5 days). He did not test these results for statistical significance, and there are not sufficient data to allow the reader to do so. Cantarovich employed three treatment protocols in his two studies. In the two protocols with the highest doses of furosemide, he found that there was significant shortening of the average duration of oliguria in the treatment group.[14,15] The structural flaws in these two studies were reviewed above. In the only randomized controlled study, Kleinknecht[50] found a nonsignificant trend favoring treatment (11.9 versus 15.6 days average duration).

Duration of azotemia. None of the controlled studies showed a significant difference in average duration of azotemia between the treatment and control groups, although in three of the studies there were slight trends favoring the treatment groups.[14,15,50]

Dialysis requirements. Beroniade[13] found that 8 of 12 treatment patients required dialysis, compared with 11 of 12 control patients. However, he did not define his criteria for dialysis, nor did he test his results for significance. However, using Beroniade's data, one may carry out a one-tailed Fisher exact test,[52] which shows that this result is not significant ($0.2<P<0.5$). Cantarovich[14,15] defined conditions for dialysis, and found that treatment patients required significantly less dialysis than control patients. Kleinknecht[50] also defined dialysis requirements, and found a nonsignificant trend favoring treatment.

Time to onset of a diuresis greater than 1,500 ml per day. In the three studies which discussed this criterion of success, it appears that high doses of furosemide significantly shorten (by about 50 percent) the average time required to achieve a diuresis greater than 1,500 ml per day.[14,15,50]

Mortality. Fewer patients died in the treatment group in Beroniade's study (3 of 12, versus 6 of 12), but he did not test these results for significance.[13] Again, the application of a one-tailed Fisher exact test shows lack of significance at the $\alpha=0.05$ level. In the other three studies, no significant differences in mortality were found between treatment and control groups, nor were trends favoring either group seen.

Discussion

More information is needed regarding the risks of using high-dose diuretic therapy in patients with ARF. It has been suggested that renal failure may be a precondition for the occurrence of diuretic-induced deafness because this underlying condition was present in all the patients studied in whom deafness occurred. However, because acute renal failure is the indication for high-dose diuretic treatment in almost all cases, renal failure may be associated with deafness only as a confounding variable. Also, synergistic ototoxicity between these diuretics and aminoglycosides has been postulated but not proved. Finally, the incidence of transient and permanent deafness occurring in patients with ARF when these diuretics are given in large doses is not known. One can only extrapolate that the incidence is probably higher than that seen in healthier patients with congestive heart failure or edema who receive conventional orally given doses of the diuretics.

Similarly, our knowledge of the possible benefits of using these two drugs in patients with oliguric ATN is incomplete. It is fairly certain that treatment with furosemide shortens the average duration of oliguria, and treated patients achieve a urine output greater than 1,500 ml per day earlier than control patients. While this earlier diuresis would facilitate volume management, it is not associated with a shorter average duration of azotemia. Thus, it appears that some treated patients convert from a state of oliguric ATN to a state of nonoliguric ATN.

Recently, Anderson and co-workers[53] showed that patients with nonoliguric ATN had a significantly lower incidence of morbidity (gastrointestinal bleeding, septicemia, acidemia, and neurological abnormalities) and mortality than patients with oliguric ATN. This difference held true for patients with spontaneous nonoliguric ATN as well as for patients in whom oliguric ATN changed to nonoliguric ATN after one or more intravenously given doses of furosemide (2 to 10 mg per kg of body weight). Of 56 patients who had oliguria, 40 received furosemide in doses of varying sizes; in 18 of these 40 there was a change to nonoliguric ATN. The patients in whom there was response to furosemide had significantly less renal impairment than those in whom there was no response to furosemide. Despite these promising findings, the authors concluded that "the value of the common clinical use of furosemide in treating the oliguric

patient remains to be determined by prospective controlled trials."[53]

It appears likely that in patients treated with furosemide, considerably fewer dialysis sessions are needed, on an average, than in control patients. In the four controlled studies, trends favoring the treatment group were present in two, and in the other two studies, differences in average dialysis requirements were significant. Because hemodialysis is expensive and associated with some morbidity, a decrease in dialysis requirements would be advantageous.

Finally, none of the four controlled studies found a significant difference in mortality between treatment and control groups. On the other hand, power analysis shows that none of these studies included enough patients to achieve statistical significance at the $\alpha = 0.05$ level, even if a large difference in mortality existed. For example, in Kleinknecht's study,[50] mortality in the control group was 12 of 33 patients, or about 35 percent. If the mortality in the treatment group were really 25 percent (a clinically important reduction), each group would require 367 patients to have an 80 percent chance ($\beta = 0.20$) of detecting such a difference at the $\alpha = 0.05$ level.[54] Stated another way, with only 33 patients in each group, mortality could drop from 35 percent in the control group to 5 percent in the treatment group, and the study would still have only a 70 percent chance ($\beta = 0.30$) of detecting this difference at the $\alpha = 0.05$ level.[54]

Summary

There is no reason to administer either ethacrynic acid or furosemide to persons as an aid to diagnosing oliguric ATN. In patients shown to have this syndrome, treatment with large doses of furosemide given intravenously, will shorten the average duration of oliguria, and shorten the time until a daily urine output of 1,500 ml occurs. Requirement for dialysis probably will be modestly decreased. However, there is no evidence from controlled studies that the average duration of azotemia is reduced by this treatment or that mortality is decreased, although these studies have large β-errors. It is possible that furosemide may convert early oliguric ATN to nonoliguric ATN, with improved prognosis for patients, although this remains to be proved in prospective controlled studies.

The known and potential benefits must be weighed against the known risks of these drugs, most importantly, the induction of permanent deafness. In doses of less than 100 mg, furosemide is probably safer than ethacrynic acid.[35] There is no reason to believe this does not hold true for larger doses as well. Using rates of administration less than 15 mg per minute probably will reduce the incidence of deafness. Thus far, this rate has not been shown to reduce the possible efficacy of furosemide in patients with ATN. While more data are needed concerning this therapeutic dilemma, physicians who decide to administer furosemide as a treatment for patients with oliguric ATN should be aware of the risks of this therapy, and strive to minimize them.

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Scientific Writing Award

THE JEAN SPENCER FELTON, MD, AWARD FOR EXCELLENCE IN SCIENTIFIC WRITING is given annually by the Western Occupational Medical Association to the author of a book, journal article or other written work important to the field of occupational health. Authors should reside in the western states, but need not belong to any particular organization. Presentation of the award will be made October 17, 1980.

Nominations should be accompanied by a copy of the written work and mailed by September 8, 1980, to Joseph LaDou, MD, Chairman, Jean Spencer Felton, MD, Award Committee, 1197 East Arques Avenue, Sunnyvale, CA 94086.

Orthodox Medicine Humanistic Medicine Holistic Health Care

IN THE DECEMBER 1979 issue the editors began a forum for discussing orthodox medicine, humanistic medicine and holistic health care. The response from readers has been so great that contributions to the forum no longer can be accepted. A future issue of the journal will carry a summary of the dialogue and discussion.

—MSMW

Holistic Medicine: Reactivation of an Old Aspiration

RAFAEL CANTON, MD

IN THE EVOLUTION of Medicine, there have been several swings of the pendulum between comprehensiveness and specialization. The holistic medicine movement can help us to make the practice of medicine more successful. Open-mindedness about treatment modalities and good human relations with patients and their families can go far toward that goal.

Historical Background

The original *medicine man* was probably a very eclectic person. He did not confine himself to either the body or the mind, nor to any subdivisions of the mind or the body. Hippocrates, Galen, Avicenna and Paracelsus used an approach that considered the whole person.[1]

In the 18th century there began a separation of the mind and the body in the field of medicine. In the 19th century and early 20th century this separation became accentuated. Physicians who treated the body acquired a great devotion to the scientific method. Physicians who treated the mind became fascinated with the discovery of the unconscious.

In the latter part of the 19th century there began a trend to unite the two artificially separated fields—the mind and the body.[2] Canon and Pavlov were very influential. Adolf Meyer introduced the term *psychobiology* as an attitude toward the individual person as a totality, in a longitudinal, rather than a cross-sectional, view. Terms such as *psychosomatic, comprehensive* or *total* medicine were introduced or revived. In 1919 Southard used the term *social psychiatry,* in a book coauthored with a social worker. The concepts of physical and mental hygiene gained acceptance. Since World War II there has been a gradual evolution of rehabilitation—physical, vocational, social, psychological. Selye's work on stress opened new vistas. Rahe, Holmes and others have attempted to measure the stressfulness of "recent life changes." The influence of type A and type B personality or behavior is being studied.

The trend to more enlightened and humane practice has continued. Forces that accelerate and shape it come from many sources. Manifestations of the trend are terms such as *holistic medicine,*[3] *integral medicine, humanistic psychology, consciousness-raising, bio-psycho-social* and so forth.

The Challenge of Holistic Medicine

Holistic or humanistic medicine is a manifestation of the desire for a better quality of life. Its beneficial effects will be in proportion to the extent to which its concerns are incorporated into the practice of the individual physician and into the practice of medicine in general. Therefore, we should retain our scientific strivings, but we should give equal importance to humanistic strivings. THE WESTERN JOURNAL OF MEDICINE is performing a valuable service in opening up its pages to input on this subject from its readers.

Physicians are faced with a dilemma. The revolution of rising expectations requires that we learn more of the facts and theories presented by the explosion of medical scientific knowledge. At the same time, it requires that we become more proficient in the *art* of medicine—handling rapport with our patients, facing complicated ethical problems, dealing with our own conscious and unconscious motivations, communicating with a patient's relatives, and the like.

The challenge is constant, vast and intricate.

Dr. Canton is in the private practice of psychiatry in Ventura, California.

Refer to: Canton R: Holistic medicine: Reactivation of an old aspiration, *In* Orthodox medicine, humanistic medicine and holistic health care—A forum. West J Med 133: 171-172, Aug 1980

The following suggestions, although very limited, may facilitate this process.

Some Practical Suggestions

- *Awareness of our limitations.* No doctor can know all that is needed to be known about every problem brought by every patient. No doctor can establish and maintain the *therapeutic alliance* with every patient. There are limits to our knowledge, empathy and compatibility. Therefore, we should be prepared to refer certain patients to a colleague, without feeling that such an event diminishes our professional stature.
- *Acceptance of moments of anger.* Even in the best of relationships, there are conflicts and misunderstandings. The doctor and the patient are better off if they accept this and deal with it constructively.
- *Repetition and feedback.* It is important to ask the patient to state, in his own words, his understanding of the doctor's words. Conversely, it helps for the doctor to paraphrase his understanding of what the patient has said. In this manner, both sides know that they have been understood. The doctor should accept also that the learning process requires repetition.
- *Meeting the patient's expectations.* The patient may have a clear preference as to how his case is handled. This can be determined by asking "How would you like me to help?", or "Is that all right with you?", or "What are your thoughts about that?" It is important to be willing to negotiate with the patient, even at the risk of being somewhat manipulated. In this manner we decrease some conscious and unconscious resistances.
- *Using the power of suggestion.* This is a strong force, for health or for illness. The patient should be told that it is a normal resource at his disposal. When the patient feels in harmony with his doctor, his morale is high. Then, the patient is more likely to follow instructions, to benefit from them, and to use the power of suggestion in a positive manner.
- *Accepting the reality of the patient's self-report.* Pain and other subjective symptoms are hard to describe. However, the most real things occur "in the minds of men." Even if the physician has no organic explanation for a symptom, he should respect it as a sincere statement of fact, as perceived by the patient.
- *Communicating with "significant others."* With the patient's consent, the physician can initiate such communication. Thus, the physician can obtain more objective information and he can exert a beneficial influence on how the family handles the illness. However, confidentiality should be maintained.
- *Open-mindedness about treatment modalities.* The human body and mind are extremely complex. The patient has a right to try other modalities. Most of the time, it is not a matter of life or death. Open-mindedness may mean making a referral, or waiting while the patient explores other modalities, or learning a technique such as acupuncture, hypnosis, biofeedback or dream interpretation.
- *The importance of pain.* Chronic or recurring pain should receive more attention from the physician. Pain is a real, widespread, and demoralizing factor. Pain is a complicated and individualized phenomenon. Its treatment requires detailed input from the patient, a multi-modal approach, patience, long-term goals and repeated encouragement to the patient.
- *Taking care of the doctor's well-being.* This means, generally, good physical and mental hygiene. The doctor should be able to *decompress* himself by indulging in occasional fantasies of anger against the patient who frustrates him. He should limit the number of especially frustrating patients, so that they do not exceed the limit of his ability to tolerate them with kindness and empathy. An overdose would be detrimental.

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Holistic Medicine and Unscientific Cults

GARRY S. BRODY, MD

MY COMPLIMENTS TO YOU for opening a forum for discussion on the current craze of holistic medicine. The last few years have seen an unusual phenomenon in the politics of health care. There

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Refer to: Brody GS: Holistic medicine and unscientific cults, *In* Orthodox medicine, humanistic medicine and holistic health care—A forum. West J Med 133:172-173, Aug 1980

has been a spate of word coinage followed by convoluted extensive and expensive debate on defining what such words mean. *Primary care* and *unnecessary surgery* have been two such catch phrases. Each of your essayists has seen fit to assign his own definition of *holistic* or *wholistic*—they cannot even agree on the spelling.

From the time of Hippocrates, medicine has taught concern for the entire patient and interpretation of man's illnesses in the light of his social and emotional circumstances as well as his physical state. The recent explosion of technological input into the physical side of medicine has led to the impression that the health establishment is mechanistic and unfeeling and solves all problems with a pill or a scalpel. But where is the hard evidence of the health professionals' turn from compassion? So much *testimonial* evidence repetitively proselytized by countercultural activists and pitchmen soon becomes interpreted as fact without any critical analysis. Most health care professionals I know are warm, caring, concerned people. Why is my testimonial not as good as Ted Kennedy's?

In the world's most technically advanced society it is a remarkable dichotomy to note the influence of the psychics, metaphysicists and faith healers. Columnist James Reston and the few early visitors to communist China single-handedly created the placebo effectiveness of acupuncture, sending the medical establishment into a convulsion of investigations to prove that it works, if it works or how it works. A few entrepreneurs in Mexico have now forced our National Institutes of Health to invest preciously scarce research dollars to see if Laetrile has any value. Add to that the cost of various state legislative efforts to legalize the apricot pit. Certainly there is a place for placebos and the *laying on of hands* but only if they are recognized for what they are.

The major concern with the holistic *movement* is that again we are opening the doors for the slick-talking entrepreneurs to prey upon the resources of the ill, the unhappy and the dissatisfied. The crime is that our foremost institutions which should be the bastions of truth and scientific method have given succor to these opportunists. Note a prestigious University of California medical school sponsoring a Category I credit international conference on "Holistic Health." The curriculum has included such presentations as "Tibetan Gong Therapy," "Autogenic Therapy," "Experiencing Spiritual Healing" and "The Use of Meditation—Visualization Techniques to Promote Healing." The faculty largely seemed to be self-credentialed, with many being founder-presidents of their own institutes of something or other, and included chiropractors, swamis, psychics and parapsychologists. True, the program also included accredited physicians, including a medical school dean, an anesthesiologist, an obstetrician and even Dr. Christian Barnard. By giving such cultists a forum the university has tacitly endorsed them, so how can we expect the uncritical public to avoid being bilked by the unscrupulous or, even worse, delaying or neglecting treatment of serious disease?

I can understand that many physicians may have forgotten the scientific method, but a university never should. Neither should THE WESTERN JOURNAL OF MEDICINE. That each person should be responsible for his own health and that the medical establishment should be cognitive and assistive of all of a patient's ills was never at issue. But the term *holistic* by virtue of the meaning imparted by common usage is lost to us, taken over by the self-styled healers and entrepreneurs.

Medicine's role toward assisting patients to take control of their own well-being should include the debunking of frauds, insisting that each new health modality at least stand the test of the scientific method. Carl Sagan has recently gotten some of the scientific establishment to begin debunking the pseudoscientists and psychic frauds such as Uri Geller, Erich Van Daniken and the Kirlian photographers. Unfortunately, our press finds more human interest in publicizing these pseudoscientists than in their debunkers. Perhaps we in medicine do not wish to be bothered with the enormous effort required to expose the unscientific cultists, but—my God—let us not embrace them.

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Medicaid in Washington State

To the Editor: The articles dealing with Medicaid in California in the June issue ("Medicaid and the Mainstream: Reassessment in the Context of the Taxpayer Revolt" and "Runaway Costs in Medi-Cal—A Myth") are of particular interest to Washington physicians because we are also grappling with the myriad problems associated with our Medicaid program.

Low reimbursement to Washington physicians has led to a situation where only 51 percent of the state's physicians will accept Medicaid patients (according to a Washington State Medical Association study, "A Program for Improvement," May 1980). Although we have not abandoned the ideal of mainstream medicine for the poor, in many parts of the state of Washington, mainstream medicine is not an option for those economically disadvantaged.

The Washington State Medical Association has been studying the issue for some months, in an attempt to come up with solutions to this very disturbing problem. We have met with the governor, the secretary of the Department of Social and Health Services and other key government officials to bring this problem to their attention. Our recommendations include not only a fee increase of 15 percent to 20 percent to assure more widespread physician participation, but also reform of the program itself to make it less onerous for physicians to participate.

Our list of recommended reforms includes instituting co-payment by recipients (although this can be accomplished only through a change in federal law) so that the needy will have an incentive to conserve medical care resources; using a single billing form (Oregon already has a single billing form for both private insurance companies and its Medicaid program); and striving seriously to improve the relationship between physicians and the Department of Social and Health Services so that the adversary climate is cooled.

While we do not have any illusions that these reforms will make the program work perfectly, we do believe they are a start toward once again trying to realize the ideal of providing mainstream medicine to the poor.

RUPERT O. BROCKMANN, MD
WSMA Medicaid Project Chairman
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Cost Control in the Nursery

To the Editor: Every now and then the Medical Service Bureau of Idaho randomly selects a sample copy of a patient's hospital bill to be sent to the attending physician for review and possible comment. By coincidence, the same mail brought such a bill to me along with the May issue of The Western Journal of Medicine, with its fine symposium on "Controlling the Cost of Health Care."

All too often such sample hospital bills are glanced at, then discarded. But this time, perhaps as a direct result of reading the articles in the Western Journal's symposium, I took a closer look at this itemized bill. One figure jumped out at me: "Nursery care, $102.00/day." Could this be a mistake, had someone made an error in moving the decimal point one space to the right? No, I was told that the amount was correct.

I was shocked, and a little outraged, on learning they were charging my patient, or her insurance carrier, more than $100 a day for a baby's bath, a weigh-in and an occasional diaper change. How long has this been going on? Clinton McGill was so right when in his article he urged that the price of every hospital service be made known to the physician at the time the service or test or medication is ordered. This price of nursery care, so far out of line, surely got my attention.

To those of us who can remember when we could buy an ice-cream cone for a nickel, and when the nursery care of the newborn infant was simply included as a part of the daily charge for maternity care of the mother, $102 a day (plus itemized charges for diapers, PKU, newborn kit,

pharmacy, etc.) does seem exorbitant. Add this sum to the mother's daily charges and we can agree that our patients have ample reason to complain.

But complain to whom? From an economist's viewpoint, Dr. Neuhauser contends that no single sector is wholly to blame. With third party payors, including the government, supplying funds for health care, our patients are quick to demand the best. In response, physicians and hospital administrations hasten to install the latest, shiniest equipment. And so our nurseries now boast of bili-lites and baby warmers, isolettes and neonatal intensive care units. It is ironic, Neuhauser observed, that since doctors and hospitals have now responded to the demands of society, regardless of cost, instead of being praised for social responsibility we are being blamed for the consequences.

The swing towards "alternate" birth facilities, home deliveries and midwifery are at least in part a result of this tremendous escalation of hospital costs. Certainly, the need for such ultrasophistication in our nurseries can be open to question.

Dr. John Moyer, the immediate Past President of the Washington State Medical Association, in commenting on a recent trip he made to England, said, "You know, in England they don't use the nurseries in the hospitals anymore; they just store things in them. They know that the baby belongs with the parents, and not in the nursery." Having observed medical practice in England firsthand, I have a strong suspicion that the cost in pounds, as much as the value of parental bonding, was a determining factor.

We physicians and our patients, unlike our English cousins, are not likely to give up our nurseries. We can point with pride to the great strides our pediatricians and neonatologists have made in salvaging premature infants and in lowering neonatal death rates. But we will grouse at the price we have to pay for well-baby care. Wise hospital administrators will, therefore, begin to take a hard look at their charges for a baby's room and board. Bassinets cannot be that costly, and these days most mothers supply the "board." At $100 a day a normal newborn baby is just being overcharged.

If we do not want our nurseries turned into storerooms we will follow Dr. McGill's suggestion to become informed, and we will not wait for third party payors to do it for us. Next, if we are really sincere about controlling costs we will raise a hue and cry about this neonatal rip-off.

What is the charge for well-baby care in *your* hospital?

E. R. W. FOX, MD
Special Editor for Idaho
Coeur d'Alene, Idaho

Insect in the External Auditory Canal

To the Editor: In the Letters section of another journal several months ago (*JAMA,* 243:331, Jan 25, 1980) Dr. Anton Schittek wrote as follows: "The conventional remedy [for a living and moving insect in the ear] is mineral oil instillation. . . . [it] works, but with a delay needed for asphyxiation of the insect. . . . Another drug, to my knowledge not described in textbooks, is 2 percent lidocaine solution. . . . It acts immediately on the insect by paralyzing it. An added bonus is that the retrieval of the insect is easier from an aqueous solution than from the mineral oil. . . . I recommend it as the method of choice. . . ."

In my early years of practice (in about 1932), a young women entered my office, saying that she thought there was an insect in her ear. It was flapping around and was driving her crazy. On examination, I could see just the wing tip of an insect which was moving around violently. I could recall no recommended treatment for this emergency. What to do? Then I remembered, as a boy on the farm, washing out ground squirrels by pouring water in their holes. So I placed the patient on her side with the "affected ear" uppermost. Then, I filled the ear with water from an eye dropper. Almost instantly the insect surfaced for air and was easily captured with my fingers.

This method is simple, requires no special solutions or instruments and can be applied by almost anyone. All one needs is water.

ROBERT A. STEVEN, MD
San Francisco

Correction: Progestin, Not Progesterone

To the Editor: The article "Ectopic Pregnancy: Current Etiology" in the March Epitome Section (West J Med 132:230, Mar 1980) contains a misnomer regarding the term progesterone.

The second paragraph refers to "progesterone-only oral contraceptives" in both the second and last sentences. *Progesterone* is not in oral contraceptives. *Progesterone* is a distinct physiologic hormone fundamental to mammalian steroid bio-

synthesis and is naturally present in the body of both sexes throughout life.

Progestin, also correctly called progestogen and progestagen, is a general term for *all* agents that biologically have progestational activity, including natural *progesterone,* and several synthetic analogues that are not natural. Maintaining the distinction between *progesterone* and *progestin* is essential to clear scientific and medical communications, because the actions of *progesterone* are different from those of other *progestins.*[1] The same differentiation should be made among other *progestins* as well.

Imprecise use of terminology should be combatted at every opportunity. It creates confusion not only in the literature but also in scientific thinking.

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EDITOR'S NOTE: *Dr. Benson's comments are appreciated. A copy-editing error resulted in "progesterone" being substituted for the correct term, "progestin."*

—MSMW

Preventive Medicine or Disease Prevention

TO THE EDITOR: We congratulate you for the May symposium "Controlling the Cost of Health Care" and the article by Dr. Chris Holmes, "Prevention: An Idea Whose Time Has Come?" (West J Med 132:381-429, 471-473, May 1980). These writings plus the earlier forum on "Orthodox Medicine, Humanistic Medicine and Holistic Health Care" indicate that you care deeply for patients. (Indeed, finding a journal that concentrates on patient care is a pleasure.)

Preventive medicine may remain a not-very-well-liked stepchild partly because of semantic problems. *Webster's Third New International Dictionary* says "medicine" is (1) A substance used in treating disease. (2) The art and science dealing with the prevention, alleviation or cure of disease. "Preventive" means preventing or making unlikely. One doubts preventive medicine is trying to prevent either 1 or 2. In fact, "disease prevention" may be a more reasonable name for the practice of decreasing the likelihood of disease. When semantically judged, internal medicine, emergency medicine, tropical medicine, orthodox medicine, humanistic medicine and holistic medicine are reasonable. Perhaps changing preventive medicine's name to a more accurate one might help us and our patients accept it better.

Still, one flaw sticks out among the above disciplines: They are all disease oriented. For years, Sidney Garfield, the founder of Kaiser-Permanente, has said he wanted a "health plan" but got a "sick plan." One wonders if our success would improve if we concentrated more on building health than attacking disease. People become rich by concentrating on becoming wealthy not by trying to cure their poverty. Similarly, trying to improve people's health in a practical, cost-effective way may be a more positive approach to medical care than trying to diagnose and attack each disease piecemeal (a perusal of a differential diagnoses book should convince many of us that our disease-oriented approach is too complex and difficult). Possibly, then we should begin studying the "eugenesis" of health in addition to the pathogenesis of disease.

Our Health Improvement Service is a step in this direction. In a few years we may know if this is more successful in making our patients healthy than our "sick plan" has been. Healthy, of course, implies absence of disease (wellness) and fullness of vigor and strength. And is this not what we physicians want for our patients and ourselves too?

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Medical Schools and Community Hospital CME

TO THE EDITOR: I read with interest an exchange of correspondence last year in the WESTERN JOURNAL: Block, "Community Hospital CME—A Missed Opportunity" (January 1979), and Covell's response under a similar title (April 1979). The interchange between the two stimulates me to take the liberty of offering these thoughts:

- The observations made by both authors are right. Inhospital continuing medical education (CME) deserves far more support than it has re-

ceived in the past; as Covell points out, medical schools increasingly are moving toward providing that support. It is by no means clear, however, that we know how to bridge the traditional town-gown division in constructive fashion.

• CME accreditation as presently practiced in most of the country does not guarantee program quality. As originally developed by the American Medical Association and implemented by most state medical associations, major attention is given to administrative/organizational factors, rather than to the crucial *educational* elements of needs-identification, formulation of goals and objectives, selection of relevant methods and evaluation of learning outcomes. Perhaps the most serious flaw in CME accreditation as now practiced is the failure to require even good-faith effort to evaluate learning outcomes. (For a detailed analysis, see my "Accreditation of CME and Public Credibility," *Bull NY Acad Med* 53:346-356, 1979.)

• While many medical schools—including Dr. Covell's—are moving to support inhospital CME, a substantial number continue to offer what the faculty think physicians need—most often, didactic transmission of factual information. Note, for example, Mason and Kappelman's 1977 survey of medical school directors of CME: 62 percent of the subjects for CME courses were selected by program organizers, and only 28 percent dealt with needs identified by the audience. *(J Med Educ* 52:341-342, 1977)

• Dr. Covell's observation about the lack of competence in educational planning among community hospital staff is well taken—as is Dr. Block's complaint that the California Medical Association (CMA) provides too little support on this matter (beyond its accreditation function). In fact, things are worse in most states than in California; CMA has offered a number of statewide conferences on CME planning and accreditation, as well as excellent workshops on use of hospital audit data for CME planning. Happily, this situation is changing. The Illinois State Medical Society initiated a trend in 1972 by establishing the Illinois Council on CME (ICCME) in collaboration with the state's eight medical schools. From its beginning, the Council's central thrust has been to teach the teachers—that is, assist CME planners to gain and improve skill in educational methods as they apply to the continuing education of physicians.

Many of your readers are familiar with ICCME products and activities: a unique set of CME planning handbooks, our annual Congress on CME, our inhospital and weekend workshops on educational methods, as well as informal advice and consultation.

It is gratifying to report that other state associations are beginning to seek their own approaches to providing the kind of support Dr. Block urges. The Iowa Medical Society has now held two annual conferences for hospital CME planners; the Colorado Council/CME—a consortium of the state association, the Colorado Foundation for Medical Care and the state university medical school—has just published a manual on CME planning that deals with that state's problems. The state medical associations of Alabama and Georgia both have professional educators on their staffs; while their major functions focus on CME accreditation and statewide CME programming, both offer advice and consultation to local hospitals. Similar examples can be found in Pennsylvania, Utah and other states.

• Mandatory CME has not yet exhibited major effect on physician performance; the immediate effect has been to increase the demand for "Category 1 credit" and for CME accreditation. It is far too early to reach a final verdict, however. If the CME accreditation process changes, likely so will the quality of CME available to American physicians, whether offered by medical schools directly or *via* their faculty members' participation in national specialty society conferences, or by community hospitals. Again, the Illinois State Medical Society—with the assistance of the Illinois Council/CME—has taken the lead. This may be the only CME accrediting agency that has denied accreditation to hospitals and other agencies (including the Illinois branch of a prestigious national voluntary health association) for failure to give adequate attention to evaluation of program effectiveness. The ISMS Committee on CME Accreditation—backed by the Society's Trustees—moved toward a more rigorous accreditation system during the period when mandatory CME for license-renewal was being inaugurated in Illinois. While accreditation (or reaccreditation) was being denied to those who refused to display skill in educational planning, the great majority of Illinois CME sponsors seeking accreditation have responded to the new system as an opportunity to learn how to do it better.

• Whatever medical schools owe to community

hospitals *(and vice versa),* surely practitioners have a right to expect professional educators—that is, medical school faculty—to devote some of their time to research on effective educational methods in community hospitals. The barrenness of the CME literature on this subject has been noted frequently. Again, with notable exceptions, medical schools have been particularly deficient in developing valid methods to assess program effectiveness and learner achievement.

I hope these few words add emphasis to the first observation of this letter: Both Dr. Block and Dr. Covell are right, and I agree with both of them. Indeed, I continue to find personal as well as professional gratification in the steadily growing consensus that the continuing education of physicians deserves much more systematic and serious attention than it has yet enjoyed, and in the ever-growing effort by a wide variety of institutions to provide that attention.

LEONARD S. STEIN, PhD
Executive Director
Illinois Council on Continuing Medical Education
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The Healer Revisited

To the Editor: Bravo, bravo, bravo to Roger Keeney Howe, MD. How brilliantly he completely encompassed the total view of medicine and "holistic" concepts in his story "A Visit from the Healer" in the June 1980 issue. His wisdom is great and he chose the best possible format for presenting his thoughts. If any serious readers have not yet read his short article I urge them to do so now.

GARY GORLICK, MD, MPH
Los Angeles

Health Care for Gay Women and Men

To the Editor: In his brief article "Treating Homosexual Patients" in the Epitomes section (132:524-525, Jun 1980), Dr. William Kapla notes that knowledge about homosexual men and women, including sexual practices and life-style issues, is a prerequisite for optimum medical care for lesbian or gay male patients. As a specific example of this principle, Dr. Kapla notes that homosexual patients appear to be at greater risk for contracting sexually transmitted disease (STD).

To my knowledge, current published findings and anecdotal information suggest that only gay *men* are especially vulnerable to STD's, particularly to some STD's that are rarely, if ever, transmitted heterosexually (such as amebiasis, giardiasis, shigellosis). Conversely, gay *women* appear to be at minimal risk for contracting STD's, especially if their sexual activities are limited to exclusively gay women.[1] And because many lesbians have a history of heterosexual activity and have borne children, or may wish to bear children in the future, the full range of gynecological medical care is relevant to the health care of gay women.[2]

Thus, while it is documented that sexually active gay men are at greater risk for certain infectious diseases than heterosexual men, the risk factors for gay women may be almost identical, if not less, than those of heterosexual women, depending on the individual woman's sexual and obstetrical histories. It therefore follows that quality health care for lesbian patients does not hinge on specific procedures or information, but instead on awareness of the fact that any female patient might be gay and as such is entitled to respectful acknowledgment of her sexual preference and the social and interpersonal stresses she may be vulnerable to, as are all members of minority groups.

LISA CAPALDINI
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'Health Care' Costs

To the Editor: There are bothersome features that demand closer scrutiny in R. A. Derzon's contribution on "health care" costs in the May 1980 issue (pages 424 through 429). There is truth in the rising costs but the role of the private sector in the cause and remedy is exaggerated. The real push was what was happening outside hospitals and medical offices. Programs that unleash enormous unpaid-for demands into medical care and other social services, and result in a general decline in the purchasing power of the dollar, are events directly attributable to those who represent us politically and those who govern us through bureaucratic procedures. All federal expenditures, not only "health expenses," continue to increase faster than revenue growth. That has been and continues to be the history of inflation.

Census Bureau statistics (1976) reveal that inflation accounted for 44 percent of the increases

of "health care" costs from 1950 to 1965. In the period from 1965 to 1975, further inflation accounted for 53 percent of the total increase.

In 1950 it is estimated that 5 percent of the gross national product (GNP) went for "health" and by 1975 the figure was 8 percent. But a more important datum, which is neglected, is that in the interval the GNP jumped fivefold (500 percent) according to Census Bureau statistics. An 8 percent portion of the GNP which increased 500 percent does not carry the grave implications of an 8 percent in a GNP that remains the same; it provides more latitude for spending for "health" and "other valued public services."

There is widespread loose usage of the term "health care" (editorial, "On Assuring Health Through Health Care," *WJM*, December 1978). This is particularly so when the term is applied to costs by government officials. Such use includes not only the pertinent medical services over which medical practitioners have a modicum of control, but also general public health measures, research grants, hospital construction, medical tuition subsidies and numerous other government programs over which private medical practitioners have very little, if any, control.

There is, of course, a place for legitimate differences of opinion, but I am annoyed at the caveats and the blaming (if I read Derzon correctly) of the practitioners—an approach that places the burden of correction for governmental inepitude upon the shoulders of the medical profession. Aside from inflation and loose terminology, and calls for our prudence and cooperation, the economic inefficiency and imprudence of subsidizing the medical care of the well-to-do and the rich under Medicare needs to be mentioned. Moreover, medicine is blamed for the high cost of legislated Medicare, when even former Chairman Wilbur D. Mills and his fellow members on the House Ways and Means Committee were shocked and noticeably chagrined "at the gross underestimates of the cost of Medicare furnished his committee by Department of Health, Education, and Welfare officials and other experts" (*Chicago Tribune,* September 11, 1967). This, of course, is the customary political approach to new programming. When Medicare costs skyrocket, is this medicine's fault? Or, what about Medicaid, legislated as a total surprise behind closed doors?

A comment by Donald J. Senese in the July 1980 issue (page 427) of *The Freeman* (Foundation for Economic Education of New York) underscores the above observations:

> The DHEW estimated that the cost for Medicare hospitalization for the first year would be less than one billion dollars. The actual cost was three billion four hundred million dollars—more than three times the original estimated cost. The tenth year cost estimate was $1.7 billion but actually was $12.6 billion or seven times the original estimate. The cost for Medicaid in 1977 was $17.1 billion or more than sixteen times the original estimate.

All this does not deny the need of truly prudent retrenchment. But, have you witnessed any *comparable* onslaughts for cost-containment in other services by the public sector? Why the overemphasis on the high cost of medical care when health is one of our society's preferred goals? There is cause for concern that the singularity of human life and human health are certainly taking the back seat in such overemphasis. (This is not a plea for the misguided application of costly medical procedures in the imprudent pursuit of a vegetative existence.) Such overemphasis involves a consideration of a new concept of ethics—new thinking of an economic balance between the life of man as an individual versus a member of society, with the scales tilted obviously in favor of the latter. The promotion of such advantage does not ennoble our concept of economics and intensifies the age-old conflict between mass society and humanist culture.

EDWARD PALMER, MD
Lake Oswego, Oregon

Refer to: Morgenstern L: Babel in medicine? (Special Communication). West J Med 133:180-181, Aug 1980

Special Communication

Babel in Medicine?

LEON MORGENSTERN, MD
Los Angeles

THERE HAS BEEN a general decline in the quality of medical speech; it has become a jargon laced with abbreviations, acronyms, slang expressions and unintelligible word contractions. Although the burgeoning medical technology is partly to blame, physicians' disrespect for grammatical and linguistic purity is principally responsible for this degenerative trend in everyday medical speech.

Babel rose when the "whole earth was one language." Babel fell when the Lord confounded language so that the people did not understand one another's speech. The language of today's medical speech has now become such a jumble of jargon, slang and dialect that the specter of Babel is now upon us.

The meteoric rise of medical technology is one of the forces behind the degenerative trend of endlessly proliferating acronyms and abbreviations. Is another force the degradation of the central character of the medical drama, the beleaguered patient, abed amidst a bewildering array of technologic weapons against disease? Have we dehumanized him to the point where instead of a whole human being he is an organ, a disease, an operation, a bed or a room?

I have noted the creeping corruption of our language with dismay, and to document its decline and fall, I have gathered some "true to life" expressions from just a few weeks of bedside rounds. The following skit is merely an illustrative sample, not at all an inclusive portrayal. Unabridged, it could be expanded to a full length play, comic in one sense, but tragic in another.

Dr. Morgenstern is Director of Surgery, Cedars-Sinai Medical Center, Los Angeles, and Clinical Professor, Department of Surgery, UCLA School of Medicine, Los Angeles.

Reprint requests to: Leon Morgenstern, MD, Department of Surgery, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Suite 8215, Los Angeles, CA 90048.

Rounds With the Chief
or
Requiem for a Noun

The Time: 7:30 AM. Now, Yesterday or Tomorrow

The Place: Megalo Medical Center, Anywhere, USA

The Characters: Chief of Service (C of S)
Five residents (R-5, R-4, R-3, R-2, R-1)

R-5: Hey, here comes the old man . . . Hi Chief!

C of S: Good morning, gentlemen. You all look fine this morning. Shall we begin?

R-5: OK. Our first patient is an appy. Came in at 3:00, pre-opped by 3:30. R-4 had him in the OR by 4:00. Do you want to describe your findings, R-4?

R-4: Nothing to add. It was an acute AP. We did it through a McBurney. We'll keep him NPO today.

C of S: Hmmmm.

R-5: Next is the gallbladder. Came in jaundiced day before yesterday. The labs are not back yet but she's had ultrasound, a CT scan, T99 Pepida and we're considering ERCP or PCT . . . .

C of S: What's the color of her stool?

R-1: We haven't gotten around to a rectal yet.

C of S: Hmmmm.

R-5: Anyway, we decided to sit on her before cholecystectomizing her. She's being worked up. Maybe we can get her on for tomorrow.

C of S: Hmmmm. Say, that patient who just walked by looks familiar. Do I know her?

R-5: That's the breast, Chief, modified radical for CA. Two positive nodes so she'll have an onco consult and be seen by radiation therapy. Hemovac is out and flaps are fine.

C of S: Hmmmm.

R-5: Our next patient is a spleen being worked up for possible splenectomy. Hematocrit was 20 so we're transfusing him up. Tentative diagnosis is myelofibrosis. Bone marrow is cooking.

C of S: Hmmmm.

R-5: Next is a trauma victim brought into the ER at 4:00 AM. R-2 will give the details.

R-2: This fella was an auto versus auto. Head injury, facial lacerations, fractured ribs, hemothorax, blunt abdominal trauma and bilateral hips. He was seen by neuro, plastic, chest, ortho, uro, and finally we were called. He had a board-like belly. We tapped him and got blood, so we opened him up after he was volume resuscitated. We couldn't find the source. He's a little antsy this morning but his vitals are OK and his crit is stable.

R-5: What does the neurosurgeon say about his head trauma?

R-2: He's waiting for the EMI.

C of S: Has the family been in?

R-2: We didn't ask. All this guy asked about was his Porsche. It was totaled.

R-5: Our next patient is a real puzzler. He presented with a mass in the neck which we biopsied yesterday but the path isn't back yet. We might get him on for Tuesday.

C of S: On what?

R-5: On the schedule, Chief. It's pretty tight these days. . . . The inflammatory bowel disease is in the next bed. She's on hyper-al and we're waiting for GI to see her. She's ambulating to the bathroom and all her labs are on the money. GI might scope her today, but if they don't, we might want to get a gastrograffin on her.

C of S: Hmmmm. Well, that's about all I have time for today. I'm 15 minutes late for my committee meeting. Looks like an interesting service. Keep that census up. Thank you.

Residents:

Thank *you,* Chief.
[*All yawn in unison*]

But let us now remove tongue from cheek to articulate a plea. The supplication is to teachers and students alike.

There has been a spate of articles[1-3] and books[4,5] on proper medical writing. Few exist for ordinary medical parlance.[6] Pleas have been made to have English as the lingua franca of the medical world, particularly with the richness of Greek and Latin terms which lend it a universality found in few other languages. But if we persist in the bastardization of the language, there will be no lingua franca for us, no "one language for the whole earth."

Teachers as well as students are the keepers of the flame. Living languages must change, but not for the worse. Babel is upon us. Let us return to the principles of clarity, accuracy and grammatical purity.

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  Former NBC Correspondent to the United Nations
- Charles Robbins
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Saturday October 4, 11:00 am

- John Naisbitt
  Pollster and Futurist

Guest Speakers

SHAHBUDIN H. RAHIMTOOLA, MD, FRCP, Los Angeles, CA
Chief, Division of Cardiology
LAC/USC Medical Center, Los Angeles

- **New Advances in the Diagnosis of Coronary Artery Diseases**
- **Coronary Artery Bypass Surgery—1980**

HERVE BYRON, MD, FACS, Englewood, New Jersey

- **Legal Aspects of Intraocular Lenses**

RALPH O. WALLERSTEIN, MD, FACP, Regent, ACP
Governor, American College of Physicians
Clinical Professor of Medicine
University of California, San Francisco

- **Polycythemia**

DONALD D. TRUNKEY, MD, San Francisco, CA
Associate Professor of Surgery
University of California, San Francisco

- **The Pathophysiology of Shock**

PHILIP NADER, MD, Galveston, Texas
Professor of Pediatrics
University of Texas, Galveston

- **Controversies in School Health**
- **Health Education and the Physician**

BERNARD L. COHEN, PhD, Pittsburgh, Pennsylvania
Professor of Physics
University of Pittsburgh

- **Health Effects of Energy Generation**

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

ELECTROMYOGRAPHY IN CLINICAL PRACTICE—Michael J. Aminoff, BSc, MD, MRCP, Associate Professor of Neurology, University of California, San Francisco. Addison-Wesley Publishing Company, Inc., Health Sciences Division, 2727 Sand Hill Road, Menlo Park, CA (94025), 1978. 216 pages, $24.00.

As the title indicates, this is a practical book for clinicians who are interested in electrodiagnosis of nerve and muscle disorders. It is concise (with only 200 pages of large print), well organized and readable. It represents the minimum a physician should know to begin to carry out and interpret routine electromyographic and nerve conduction studies. The content is accurate and well referenced. This book therefore provides a suitable introduction to this field.

The first chapters review the fundamental physiologic principles of nerve and muscle on which this form of investigation depends, including the organization of motor units. A chapter on the essential electrical apparatus provides the necessary background in a simple and straightforward manner. Then the general principles and clinical aspects of electromyography are presented, the latter consisting of much too brief clinical accounts of the various pathological entities encountered in this kind of study. Another chapter provides a similar shopping list of peripheral nerve disorders. Fortunately, references are provided on most of the conditions described for those who wish to learn more elsewhere about a particular entity. After an adequate account of the general aspects of nerve conduction studies, two particularly welcome chapters follow which describe the practical considerations involved in testing of commonly studied nerves in the upper and lower limbs, respectively. The last two chapters concern clinical electrodiagnostic studies of the facial nerve and of neuromuscular transmission.

This book can be recommended to those physicians who are looking for a short but accurate and practical introduction to clinical electromyography.

JOHN C. KEESEY, MD
Director, Electromyography Laboratory
UCLA Center for Health Sciences
Los Angeles

* * *

INHERITED DISORDERS OF THE SKELETON—Peter Beighton, MD, PhD, FRCP(Ed), DCH, Professor of Human Genetics, University of Cape Town, Consultant in Medical Genetics, Groote Schuur Hospital, Cape Town, South Africa—in the series GENETICS IN MEDICINE AND SURGERY—General Editor: Alan E. H. Emery, MD, PhD, DSc, FRCP(E), MFCM, FRS(E), Professor of Human Genetics, University of Edinburgh. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 267 pages, $38.00.

Peter Beighton's pithy 267-page book is an excellent reference source for persons interested in the management and genetic counseling of families with inherited disorders of the skeleton. Brief coverage of skeletal disorders with nongenetic causes makes the volume a handy tool for clinical geneticists, orthopedists and birth defect specialists in ruling out differential diagnoses.

Inherited Disorders of the Skeleton is one of a series generated by Alan E. H. Emery which is designed to provide concise and reliable information about the hereditary nature of various groups of disorders. The book has 18 chapters and covers osteochondrodysplasias, disorders of increased and decreased bone density, mucopolysaccharidoses, mucolipidoses and sphingolipidoses, skeletal dysostoses, stiff joint syndromes, disorders of specific limbs or digital dysplasias and synostoses, connective disorders and primary disturbances of growth. The prodigious breadth of the little book even surpasses the classic work by Langer, Spranger and Wiedemann, but it obviously must accede to *Bone Dysplasias* in terms of depth.

The readable accounts, based on clinical cases personally examined by Beighton in clinics in South Africa, cover a wide spectrum of skeletal dysplasias. The glossary of anatomical, orthopedic and genetic terms, an appendix of the 1970 Paris nomenclature for constitutional disorders of bone (though an updated 1976 version would have been preferable), numerous illustrations and a detailed bibliography at the end of each chapter make this volume accessible to medically-trained persons who do not necessarily have a strong background in human genetics.

Its clinical illustrations are not only good, but are most refreshing, drawing from a new patient population. The illustrations alone are enough to make the work a great contribution to the field of medicine. The paucity of radiographs, on the other hand, and their relatively poor quality, force one to consult other literature in order to get a clear diagnostic picture.

On the whole, the organization is quite logical. Minor criticisms could be made about the organization and the accuracy of recurrence risk figures: One of the problems with the chondrodystrophies is getting a handle on differential diagnoses. There is not yet a clean and logical system. In this book the uninitiated might be confused, for example, by the placement of "achondroplasia" in the seemingly ambiguous category "Skeletal Dysplasias Without Significant Spinal Involvement." Second, the recurrence risk of spina bifida and anencephaly to siblings of patients with multiple vertebral anomalies quoted by Beighton (reference Wynne-Davis, 1975) is not entirely accurate. Wynne-Davis gives a range of 5 percent to 10 percent recurrence risk, not a flat 10 percent as cited by Beighton (page 171).

A final criticism is raised by Beighton himself in the preface. Because of the rapid expansion of the field of inherited disorders of the skeleton, and medical genetics in general, the book was out of date even before it could reach the press. He states "It is axiomatic that the period of time necessary for the preparation of a book always exceeds the author's initial forecast."

Nonetheless, this book should prove most valuable as a launching pad for all those involved in the care of families with skeletal disorders. The author's expertise and style of writing are certainly to be commended. As Beighton's preface clearly points out, however, the "detailed consideration [of pertinent clinical and radiological features] is outside the scope of this book, and no attempt has been made to review them in depth." Thus, a family physician caring for a patient with a skeletal disorder must seek a more complete understanding of that specific condition through further reading of the references provided in order to give comprehensive care.

SUSAN D. REED, *Genetics Associate*
University of Washington Clinical Genetic Services

JUDITH G. HALL, MD
Head, Division of Medical Genetics
Children's Orthopedic Hospital and Medical Center
Assocate Professor, Medicine and Pediatrics
University of Washington School of Medicine
Seattle

in memoriam

California Medical Association

Arrieta, Jose Humberto, San Francisco. Died October 14, 1979, aged 71. Graduate of the Universidad de El Salvador Facultad de Medicina, Salvador, 1935. Licensed in California in 1945. Dr. Arrieta was a member of the San Francisco Medical Society.

Beauchamp, Harvey D., Sonora. Died in 1980 in Sonora, aged 75. Graduate of St. Louis University School of Medicine, 1932. Licensed in California in 1932. Dr. Beauchamp was a retired member of the San Joaquin County Medical Society.

Demaree, Eugene W., Three Rivers. Died June 2, 1980, aged 78. Graduate of Rush Medical College, Chicago, 1926. Licensed in California in 1941. Dr. Demaree was a member of the Los Angeles County Medical Association.

Dorsey, John W., Long Beach. Died May 26, 1980, aged 67. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1937. Licensed in California in 1946. Dr. Dorsey was a member of the Los Angeles County Medical Association.

Francoz, Marius A., San Francisco. Died June 10, 1980, aged 88. Graduate of Hahnemann Medical College of the Pacific, San Francisco, 1917. Licensed in California in 1917. Dr. Francoz was a retired member of the San Francisco Medical Society.

Gaffney, Genevieve F. (Genevieve F. Gaffney Markson), San Francisco. Died June 24, 1980 in San Francisco, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1934. Licensed in California in 1934. Dr. Gaffney was a retired member of the San Francisco Medical Society.

Giles, Frances, Hollywood. Died April 25, 1980, aged 86. Graduate of Rush Medical College, Chicago, 1923. Licensed in California in 1926. Dr. Giles was a member of the Los Angeles County Medical Association.

Gospe, Sidney M., San Francisco. Died June 21, 1980 in San Francisco, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Dr. Gospe was a member of the San Francisco Medical Society.

Hadsall, Franklin Job, Merced. Died August 28, 1979 in Porterville, aged 40. Graduate of the University of California, Los Angeles, School of Medicine, 1965. Licensed in California in 1966. Dr. Hadsall was a member of the Merced-Mariposa Medical Society.

Johnson, Harvey Starkweather, Yucca Valley, California. Died May 5, 1980 in Quartzsite, Arizona, aged 75. Graduate of Northwestern University Medical School, Chicago, 1933. Licensed in California in 1933. Dr. Johnson was a member of the Los Angeles County Medical Association.

Kennedy, Raymond B., Jr, Mountain View. Drowned May 21, 1980 while swimming off the coast of Indonesia, aged 34. Graduate of the University of Tennessee College of Medicine, Memphis, 1969. Licensed in California in 1970. Dr. Kennedy was a member of the Santa Clara County Medical Society.

Landry, Bruce V., San Jose. Died June 16, 1980 in San Jose, aged 58. Graduate of the University of California Medical School, Berkeley-San Francisco, 1946. Licensed in California in 1946. Dr. Landry was a member of the Santa Clara County Medical Society.

Markus, Edwin H., Oakland. Died May 18, 1980, aged 69. Graduate of Wayne University College of Medicine, Detroit, 1938. Licensed in California in 1948. Dr. Markus was a member of the Alameda-Contra Costa Medical Association.

Schecter, John A., Rocklin. Died June 24, 1980 in Roseville of heart disease, aged 50. Graduate of Indiana University School of Medicine, Indianapolis, 1954. Licensed in California in 1954. Dr. Schecter was a member of the Placer-Nevada County Medical Society.

Ullrich, Fred D., La Jolla. Died June 11, 1980 in Hemet, aged 81. Graduate of Northwestern University Medical School, Chicago, 1929. Licensed in California in 1931. Dr. Ullrich was a retired member of the San Diego County Medical Society.

Vizzard, William R., Sr, Ross. Died June 9, 1980 in Greenbrae, aged 81. Graduate of St. Louis University of Medicine, 1926. Licensed in California in 1926. Dr. Vizzard was a retired member of the San Francisco Medical Society.

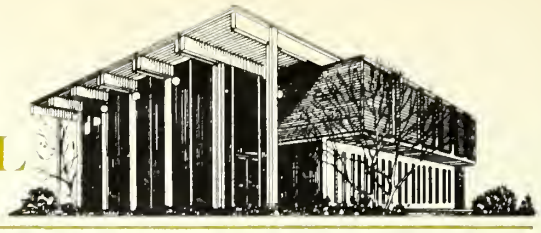
Utah State Medical Association

Cannon, J. Floyd, Salt Lake City. Died May 19, 1980 in Salt Lake City, aged 71. Graduate of George Washington University School of Medicine, Washington, DC, 1941. Licensed in Utah in 1943. Dr. Cannon was a member of the Salt Lake County Medical Society.

Evans, Dean C., Fillmore. Died June 6, 1980 in Provo, aged 83. Graduate of Western Reserve University School of Medicine, Cleveland, 1924. Licensed in Utah in 1925. Dr. Evans was a member of the Washington County Medical Society.

Richards, Ralph C., Salt Lake City. Died June 18, 1980 in Salt Lake City, aged 58. Graduate of the University of Utah College of Medicine, Salt Lake City, 1945. Licensed in Utah in 1946. Dr. Richards was a member of the Salt Lake County Medical Society.

UTAH STATE MEDICAL ASSOCIATION



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WEDNESDAY, OCTOBER 1

Course No. 1

INFLAMMATORY BOWEL DISEASE

GILBERT L. WRIGHT, MD, and
J. KENT NELSON, MD, Co-Moderators

2:00 pm

INTRODUCTION

GILBERT L. WRIGHT, MD, and
J. KENT NELSON, MD

I. Diverticular Disease

2:10 pm

PATHOGENESIS, Workup and Medical Treatment

EDWIN ENGLERT, Jr, MD
Professor of Medicine
University of Utah College of Medicine
Salt Lake City, Utah

2:25 pm

INDICATIONS AND TYPES OF SURGERY FOR DIVERTICULAR DISEASE

RUPERT B. TURNBULL, Jr, MD
Department of Colon and Rectal Surgery
Santa Barbara Medical Foundation Clinic
Santa Barbara, California

II. Crohn's Disease and Chronic Ulcerative Colitis

2:55 pm

SIMILARITIES AND DIFFERENCES IN CLINICAL COURSE, COMPLICATIONS, GASTROENTEROLOGIC WORKUP AND MEDICAL TREATMENT

G. KENNETH JOHNSON, MD
Ogden, Utah

3:10 pm

RADIOLOGY IN CROHN'S DISEASE AND ULCERATIVE COLITIS

JAMES A. NELSON, MD
Professor of Radiology
University of Utah College of Medicine
Salt Lake City, Utah

3:20 pm

BREAK

3:30 pm

WHEN MEDICAL TREATMENT GIVES WAY TO SURGERY WHICH OPERATION, WHEN AND WHY?

RUPERT B. TURNBULL, Jr, MD
Santa Barbara, California

III. Approach to Acute Infectious Enterocolitis

4:00 pm

BACTERIAL DYSENTERY AND ANTIBIOTIC COLITIS OR PHYSICIANS CREATE MORE PROBLEMS THAN THEY CURE

J. KENT NELSON, MD
Salt Lake City, Utah

4:10 pm

TRAVELERS DIARRHEA—A RUNNING TRAVELOGUE

EDWIN ENGLERT, Jr, MD
Salt Lake City, Utah

Course No. 2

COMMON PSYCHIATRIC PROBLEMS

DAVID L. McCANN, MD, Moderator

Wednesday (continued)

2:00 pm

TREATMENT OF DEPRESSION

DAVID L. McCANN, MD
Salt Lake City, Utah

2:45 pm

BREAK

3:00 pm

STRESSES FOR DOCTORS AND THEIR FAMILIES

CARLOS N. MADSEN, MD
Salt Lake City, Utah

4:00 pm

HYSTERIA AND SELF-HYPNOTIC DISORDERS

EUGENE L. BLISS, MD
Professor of Psychiatry
University of Utah College of Medicine
Salt Lake City, Utah

THURSDAY, OCTOBER 2

Course No. 3

VULVAR AND VAGINAL INFLAMMATORY DISORDERS

RICHARD M. HEBERTSON, MD, Moderator

9:00 am

HERPES GENITALIS—Diagnosis and Significance

RAYMOND H. KAUFMAN, MD

ERNST W. BERTNER, Professor and Chairman
Department of Obstetrics and Gynecology
Baylor College of Medicine
Texas Medical Center
Houston, Texas

9:40 am

VULVAR DYSTROPHIES—DIAGNOSIS AND TREATMENT

DUANE E. TOWNSEND, MD
Cedars-Sinai Medical Tower
Los Angeles, California

10:10 am

BREAK

10:30 am

DIAGNOSIS AND TREATMENT OF REFRACTORY VAGINITIS

RAYMOND H. KAUFMAN, MD
Houston, Texas

11:15 am

VULVAR INTRAEPITHELIAL NEOPLASIA—DIAGNOSIS AND MODERN THERAPY "LASER"

DUANE E. TOWNSEND, MD
Los Angeles, California

12:00 noon

SPECIAL LUNCH—Grand Ballroom, Hotel Utah
THIRD ANNUAL SKAGGS LUNCHEON

LITTLE ORPHAN ANNIE SYNDROME AND OTHER COPING STYLES IN HEALTH AND CHRONIC DISEASE

RICHARD S. FARR, MD
Senior Staff Physician
National Jewish Hospital and Research Center, and
Professor of Medicine
University of Colorado Health Science Center
Denver, Colorado

Thursday (continued)

Hopes, Helps and Hazards of Estrogen Therapy

2:00 pm

THE HOPES

A. MARSH POULSON, MD
Salt Lake City, Utah

2:30 pm

THE HELPS

WILLIAM R. KEYE, Jr, MD
Salt Lake City, Utah

3:00 pm

BREAK

3:15 pm

THE HAZARDS

RICHARD J. WORLEY, MD
Salt Lake City, Utah

Course No. 4

CORONARY ARTERY DISEASE

ROBERT B. WRAY, MD, Moderator

I. Coronary Bypass Surgery—1980

9:00 am

FROM THE CARDIOLOGIST'S VIEWPOINT

MICHAEL J. PREECE, MD
Salt Lake City, Utah

9:30 am

FROM THE CARDIAC SURGEON'S VIEWPOINT

EDWIN C. McGOUGH, MD
Salt Lake City, Utah

10:00 am

FROM THE PHYSICIAN-PATIENT VIEWPOINT

HIROSHI KUIDA, MD
Professor, Department of Internal Medicine
University of Utah College of Medicine
Salt Lake City, Utah

10:15 am

QUESTIONS

10:30 am

BREAK

II. Myocardial Scans

10:45 am

PRINCIPLES OF MYOCARDIAL SCANNING

DENNIS M. WELCH, MD
Assistant Professor, Department of Radiology
University of Utah College of Medicine
Salt Lake City, Utah

11:05 am

UTILITY OF MYOCARDIAL SCANS

STEVEN C. KLAUSNER, MD
Assistant Professor, Department of Internal Med
University of Utah, and
Cardiology Division, LDS Hospital
Salt Lake City, Utah

11:25 am

QUESTIONS

Thursday (continued)

III. Aspirin and Myocardial Infarction

11:35 am

DOES ASPIRIN PREVENT MYOCARDIAL INFARCTION?

ALLAN H. BARKER, MD
Salt Lake City, Utah

Course No. 5

CONCEPTS OF ADOLESCENT MEDICINE

ARTHUR B. ELSTER, MD, Moderator

9:00 am

CONTRACEPTION FOR ADOLESCENTS

Participants:
DONALD P. ORR, MD
Assistant Professor of Pediatrics and Social Ecology
Director of Adolescent Services
University of California, Irvine
Orange, California

MAURICE G. EMERY, PharmD
Department of Pharmacy Practice
University of Utah Medical Center
Salt Lake City, Utah

JULIAN E. DeLIA, MD
Assistant Professor of Obstetrics and Gynecology
University of Utah College of Medicine, and
Medical Director, Family Planning Program
Utah State Division of Health
Salt Lake City, Utah

10:30 am

BREAK

10:45 am

COMMON MEDICAL AND PSYCHOSOCIAL PROBLEMS OF ADOLESCENTS

DONALD P. ORR, MD
Orange, California

ARTHUR B. ELSTER, MD
Director of Adolescent Medicine
University of Utah College of Medicine
Salt Lake City, Utah

Course No. 6

COMMON DIAGNOSTIC AND THERAPEUTIC PITFALLS IN CHEST DISEASE

LORIMER T. CHRISTENSEN, MD, Moderator

2:00 pm

COMMON DIAGNOSTIC AND THERAPEUTIC PITFALLS IN CHEST DISEASE—CHILDREN

GARY S. RACHELEFSKY, MD
Associate Clinical Professor of Pediatrics and
Co-Director, Pediatric Allergy Clinic
UCLA School of Medicine
Los Angeles, California

3:00 pm

BREAK

3:10 pm

COMMON DIAGNOSTIC AND THERAPEUTIC PITFALLS IN CHEST DISEASE—ADULTS

CHARLES SCOGGIN, MD
Associate Professor, Division of Pulmonary Sciences
University of Colorado Health Sciences Center
Denver, Colorado

Course No. 7

DIAGNOSIS AND TREATMENT OF LOW BACK PAIN

ROBERT F. MOSELEY, MD, Moderator

2:00 pm

NONORTHOPEDIC LOW BACK PAIN

R. CHAD HALVERSEN, MD
Salt Lake City, Utah

2:45 pm

NEUROLOGICAL SOURCES OF PAIN: NERVE IMPINGEMENT SYNDROMES—ETIOLOGIES AND TREATMENT

A. PETER HEILBRUN, MD
Associate Professor of Surgery
University of Utah College of Medicine
Salt Lake City, Utah

3:30 pm

BREAK

Thursday (continued)

3:45 pm

MUSCULOSKELETAL SOURCES OF PAIN: BONE AND JOINT, LIGAMENT, MUSCLE—ETIOLOGIES AND TREATMENT

STANLEY J. BIGOS, MD
Department of Orthopedics
University of Utah College of Medicine
Salt Lake City, Utah

Thursday (continued)

4:30 pm

EMOTIONAL SOURCES OF PAIN: EMOTIONAL-PSYCHIATRIC AND SOCIAL—ETIOLOGIES AND TREATMENT

JAMES R. WHITTEN, MD
Salt Lake City, Utah

2:00 pm-5:00 pm THURSDAY, OCTOBER 2
9:00 am-12:00 noon FRIDAY, OCTOBER 3

Course No. 8 FAMILY PRACTICE WORKSHOP—MINI COURSES

ROBERT M. PAYNE, MD and ROLF K. NALEY, MD, Co-Moderators

Subjects	Course Director	Time Thursday	Time Friday
ARTHRITIS	H. JAMES WILLIAMS, MD Salt Lake City, Utah	2:00-3:00 pm	9:00-10:00 am
PSYCHIATRY	DAVID WOOD, MD Salt Lake City, Utah	3:00-4:00 pm	10:00-11:00 am
OPHTHALMOLOGY	GEORGE C. PINGREE, MD Murray, Utah	4:00-5:00 pm	
	RICHARD A. ALDOUS, MD Salt Lake City, Utah		11:00-12:00 noo
UROLOGY	DOUGLAS S. DAHL, MD Salt Lake City, Utah	2:00-3:00 pm	9:00-10:00 am
OBSTETRICS/GYNECOLOGY	ANTHON E. ANDERSON, MD Murray, Utah	3:00-4:00 pm	10:00-11:00 am
ORTHOPEDICS	DAVID J. HOWE, MD Salt Lake City, Utah	4:00-5:00 pm	11:00-12:00 noo

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FRIDAY, OCTOBER 3

Course No. 9

PERSPECTIVES IN HYPERTENSION

H. ALLAN BLOOMER, MD, Moderator

9:00 am

The first portion of the course will be directed to short lectures on the recognition, evaluation and treatment of hypertension in an office setting.

EVALUATION OF THE HYPERTENSIVE PATIENT

RICHARD G. LAMBERT, MD
Salt Lake City, Utah

DRUG TREATMENT OF HYPERTENSION

H. ALLAN BLOOMER, MD
Salt Lake City, Utah

SIDE EFFECTS OF THERAPY

RICHARD G. LAMBERT, MD
Salt Lake City, Utah

RESISTANT HYPERTENSION

H. ALLAN BLOOMER, MD
Salt Lake City, Utah

HYPERTENSION IN CHILDREN AND ADOLESCENTS

RICHARD L. SIEGLER, MD
Salt Lake City, Utah

Course No. 10

OPHTHALMOLOGY TODAY

GEORGE H. PINGREE, MD, Moderator

9:00 am

DIFFERENTIAL DIAGNOSIS OF SUPERFICIAL LESIONS OF THE CORNEA AND LIMBUS

THOMAS H. PETTIT, MD
Professor of Ophthalmology
Chief, Corneal External Disease Service
Jules Stein Eye Institute
UCLA School of Medicine
Los Angeles, California

Friday (continued)

10:00 am

INTRAOCULAR LENS SAFETY, EFFICACY AND ALTERNATIVES

RANDALL J. OLSON, MD
Chairman, Department of Ophthalmology
University of Utah College of Medicine
Salt Lake City, Utah

11:00 am

GENERAL DISCUSSION: Questions and Answers

Course No. 11

TREATMENT OF NEUROLOGICAL DISORDERS

JACK H. PETAJAN, MD, Moderator

9:00 am

EPILEPSY

FUMISUKE MATSUO, MD
Associate Professor of Neurology
University of Utah College of Medicine
Salt Lake City, Utah

9:45 am

HEADACHE AT ALL AGES

JOEL A. THOMPSON, MD
Assistant Professor of Pediatrics
Primary Medical Center
Salt Lake City, Utah

10:30 am

BREAK

10:45 am

MOVEMENT DISORDERS

FRED A. ZITER, MD
Professor of Neurology
University of Utah College of Medicine
Salt Lake City, Utah

11:15 am

MYASTHENIA GRAVIS, MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE DISORDERS

JACK H. PETAJAN, MD
Professor of Neurology
University of Utah College of Medicine
Salt Lake City, Utah

For further information about the scientific program contact:
UTAH STATE MEDICAL ASSOCIATION, 540 East Fifth South, Salt Lake City, Utah 84102, (801) 355-7477.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

AMA DRUG EVALUATIONS—Fourth Edition—AMA Department of Drugs in cooperation with the American Society for Clinical Pharmacology and Therapeutics—American Medical Association, 1980. 1,470 pages, $48. May be obtained from Order Dept., OP-075, P.O. Box 821, Monroe, WI 53566; also distributed by John Wiley & Sons to book stores and distributors.

ANTICONVULSANT THERAPY: Pharmacological Basis and Practice—Second Edition—Mervyn J. Eadie, MD, PhD (Queensland), FRACP, Professor of Clinical Neurology and Neuropharmacology, University of Queensland, Neurologist, Royal Brisbane Hospital; and John H. Tyrer, MD (Sydney), FRCP (Lond), FRCP (Edin), FRACP, Professor of Medicine, University of Queensland, Senior Neurologist, Royal Brisbane Hospital, Honorary Consulting Physician, Mater Misericordiae Hospital, Brisbane. Churchill Livingstone Inc., 19 West 44th Street, New York, NY (10036), 1980. 338 pages, no price given.

BASIC FIRST AID—Second Edition: Books 1 thru 4—American Red Cross, 1979. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017). 790 pages, $5.25.

BEYOND SURVIVAL—J. Pat Tokarz, MD; William Bremer, MD; Ken Peters, MD, and contributing authors: John-Henry Pfifferling, PhD, and Jesse Viner, MD, Workgroup on Physician Well-Being, Resident Physicians Section, AMA, Chicago. American Medical Association, 535 N. Dearborn St., Chicago (60610), 1979. 125 pages (paperback). (Order from Order Dept. OP-083, AMA, P.O. Box 821, Monroe, WI (53566), price available upon request.)

THE BODY OF LIFE—Thomas Hanna. Alfred A. Knopf, Inc., New York, 1979, 1980. Distributed by Random House, Inc., New York. 203 pages, $9.95.

CLINICAL STRATEGIES IN ISCHEMIC HEART DISEASE—New Concepts and Current Controversies—Edited by Eliot Corday, MD, Clinical Professor of Medicine, University of California, Los Angeles, School of Medicine, and Senior Attending Physician and Senior Research Scientist, Cedars-Sinai Medical Center, Los Angeles; and H. J. C. Swan, MB, PhD, FRCP, FACC, Professor of Medicine, University of California, Los Angeles, School of Medicine, and Director of Cardiology, Cedars-Sinai Medical Center, Los Angeles. Williams & Wilkins, 428 E. Preston St., Baltimore (21202), 1979, 611 pages, no price given.

CONTINUING LEARNING IN THE PROFESSIONS—Cyril O. Houle, senior program consultant, W. K. Kellogg Foundation; and professor emeritus of education, University of Chicago. Jossey-Bass Publishers, 433 California Street, San Francisco (94104), and Jossey-Bass Limited, 28 Banner St., London EC1Y 8QE, 1980, 390 pages, $15.95.

THE DEVELOPMENT OF THE INFANT AND YOUNG CHILD: Normal and Abnormal—Seventh Edition—R. S. Illingworth, MD, FRCP, DPH, DCH, Hon MD Sheffield, Hon DSc Baghdad, Emeritus Professor of Child Health, The University of Sheffield; Formerly Paediatrician, The Children's Hospital, Sheffield, and the Jessop Hospital for Women, Sheffield. Churchill Livingstone Inc., 19 West 44th Street, New York City (10036), 1980, 320 pages, no price given.

EPIDEMIOLOGY IN MEDICAL PRACTICE—Second Edition—D. J. P. Barker, BSc, MD, PhD, FRCP, MFCM, Reader in Clinical Epidemiology, University of Southampton, Honorary Consultant Physician, Royal South Hants Hospital; and G. Rose, MA, DM, FRCP, FFCM, Professor of Epidemiology, London School of Hygiene and Tropical Medicine, Honorary Consultant Physician, St. Mary's Hospital, London. Churchill Livingstone Inc., 72 Fifth Avenue, New York City (10011), 1979, 151 pages, no price given.

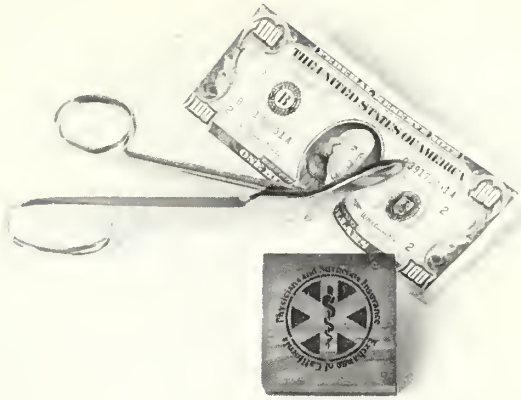
HANDBOOK OF OBSTETRICS & GYNECOLOGY—Seventh Edition—Ralph C. Benson, MD, Clinical Professor of Obstetrics and Gynecology and Emeritus Chairman, Department of Obstetrics and Gynecology, University of Oregon Health Sciences Center, Portland. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 808 pages, $10.00.

HEALTH STATISTICS—A Guide to Information Sources—Volume 4 in the Health Affairs Information Guide Series: Frieda O. Weise, Head, Public Services Unit, Reference Section, National Library of Medicine, Bethesda, Maryland. Gale Research Company, Book Tower, Detroit, MI (48226), 1980. 137 pages, $28.00.

HEART ATTACK! A Question and Answer Book—Oscar Roth, MD, Clinical Professor of Medicine, Yale University School of Medicine, Director, Coronary Care Unit and Department of Electrocardiography, Hospital of St. Raphael, Consulting Cardiologist, New Britain General Hospital, Milford General Hospital, West Haven Veterans Hospital, Rocky Hill Veterans Home and Hospital; with Lawrence Galton. Contemporary Books, Inc., 180 North Michigan Avenue, Chicago, IL (60601), 1978. 262 pages, $4.95.

HUMANIZING HEALTH CARE—Task of the Patient Representative—Norma Shaw Hogan, MPS, Director of Patient Representative Department, Northwestern Memorial Hospital, Chicago. Medical Economics, (DPRJ9), Box 157, Florence, KY (41042), 1980. 190 pages, $10.95, plus $1 handling charge (paperback).

MANAGEMENT OF HIGH-RISK PREGNANCY—Edited by John T. Queenan, MD, Professor and Chairman, Department of Obstetrics and Gynecology, Georgetown University School of Medicine. Medical Economics Company, Oradell, NJ (07649), 1980. 705 pages, $35.00.



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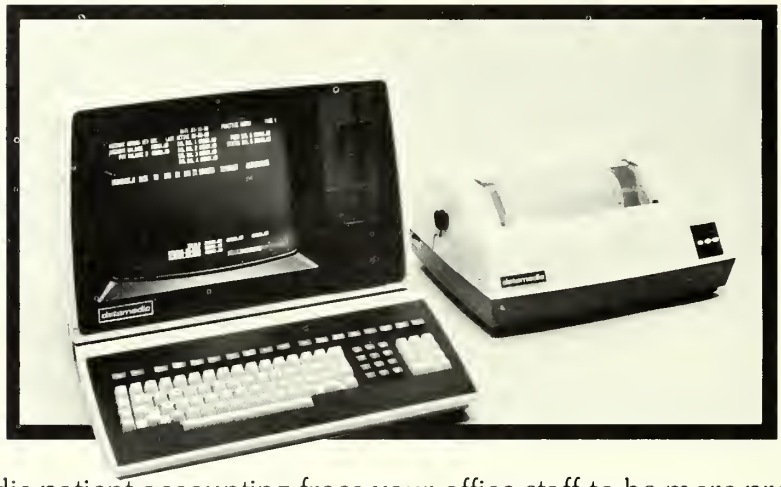

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ANESTHESIOLOGY

October 3-5—**Anesthesia Specialties.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Friday-Sunday. 10½ hrs. $90, AEF member; $165, nonmember. Contact: Walter H. Comer, MD, AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

October 26-28—**Anesthesia and Cardiopulmonary Disease.** Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Sunday-Tuesday. 11 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

November 8-9—**American Society of Anesthesiologists—Refresher Course.** Hilton, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

December 12-14—**Anesthesia: Before and After.** Tucson Hospitals Medical Education Program at Canyon Hotel, Palm Springs. Friday-Sunday. $150. Contact: James P. Angiulo, MD, Kino Community Hosp., 2800 E. Ajo Way, Tucson, AZ 85713.

CANCER

September 6-7—**2nd Annual Preventive Oncology: Nutrition and Cancer.** UCSF and No. Calif. Cancer Program. Saturday-Sunday. $130. Contact: UCSF, Cont. Ed. Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

October 9-11—**American Cancer Society.** Hilton, Los Angeles. Thursday-Saturday. Contact: N. G. Bolliglieri, MD, ACS, 777 Third Ave., New York 10017.

October 24-26—**Cancer and Enzymes.** UCSD at Vacation Village, San Diego. Friday-Sunday.

October 27-29—**4th Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. 22 hrs. $300. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

November 6-8—**Current Concepts in Cancer Diagnosis.** UCLA. Thursday-Saturday.

November 7-8—**Cancer Prevention and Screening.** Claire Zellerbach Saroni Tumor Institute of Mt. Zion Hospital and Medical Center at Holiday Inn on Union Square, San Francisco. Friday-Saturday. 10 hrs. $125 before September 15; $150 thereafter. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

EMERGENCY MEDICINE

August 25-29—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

September 6-7—**Advanced Cardiac Life Support Workshop.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Saturday-Sunday. 16 hrs. $125. Contact: Education Dept. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

September 18—**Abdominal Trauma.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 3-4—**Postgraduate Institute on Emergency Medicine—5th Annual.** UCLA at Miramar-Hilton, Santa Monica. Friday-Saturday. 14 hrs. $170.

October 9-February 5—**Management of Pre-Hospital Emergencies.** UCLA. 5 Thursday evenings.

October 13-17—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

October 16—**Dermatology in the Emergency Department.** UCSD. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 20-31—**Intensive Review of Emergency Medicine.** USC. Two weeks.

November 3-5—**Postgraduate Institute for Emergency Physicians, Symposium IV.** UCSD at Hilton, San Diego. Monday-Wednesday.

November 20—**Clinical Pharmacology in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Irvine 92717. (714) 833-5414, Fee and Information office or (714) 833-5526, 5542, Continuing Education in Health Sciences.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

December 8-12—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

December 10—**Emergency Medicine.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

MEDICINE

August 15-17—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

August 15-20—**Neuropsychiatric Issues in the Law, Education and Medicine.** See Psychiatry, August 15-20.

September 5—**13th Annual Symposium on Kidney Disease—Endocrine and Metabolic Functions of the Kidney.** Kidney Foundation of Northern Calif. at Fairchild Auditorium, Stanford Univ. Sch. of Med., Stanford. Friday. 6 hrs. $45. Contact: William Arnopp, Exec. Dir., KFNC, 100 S. Ellsworth Ave., Ste. 305, San Mateo 94401. (415) 347-6646.

September 10—**Hematuria—An Approach to Diagnosis and Therapy.** LLU. Wednesday. 4 hrs. $30.

September 10—**Sexually Transmitted Hepatitis: The Fact of Life.** DREW at Pacific Design Center, West Hollywood. Wednesday. 6 hrs. $25. Write: DREW or telephone: Loren Senseman, (213) 974-7275.

September 15-17—**3rd Annual Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Monday-Wednesday. 20 hrs. $200.

September 17-18—**48th Annual Fall Symposium and 13th Annual George C. Griffith Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Wednesday-Thursday. 13 hrs. $100, member of any heart assn.; $125, nonmember. Contact: Mary Frances Flynn, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231, ext. 59.

September 18-19—**Advances in Cardiovascular Therapies.** UCD at Sahara Tahoe, Stateline. Thursday-Friday. 9 hrs. $20.

September 24—**Renal Conference.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

September 25-26—**Annual Physicians' Symposium.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Kari Olila, AHA, 421 Powell St., San Francisco 94102. (415) 433-2273.

September 25-28—**American Society of Ophthalmologic and Otolaryngologic Allergy—Annual Meeting.** Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: William King, MD, 1415 3rd St., Corpus Christi, TX 78404.

September 26-27—**American Society of Internal Medicine.** Islandia Hyatt, San Diego. Friday-Saturday. Contact: ASIM, 2550 M St. NW, Suite 620, Washington, DC 20037.

September 26-27—**Dermatology for the Primary Care Physician.** UCD at Holiday Inn, Napa Valley. Friday-Saturday. 11½ hrs.

September 26-28—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Hyatt on Union Square, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

September 27—**Management of Common Lung Problems.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 6½ hours. $35.

September 27-28—**Recent Advances in Cardiology.** The Center Foundation, Los Angeles. Saturday-Sunday. 12 hrs. $250. Contact: Michael Urban, Dir., Cont. Med. Ed., The Center Fndn., 7165 Sunset Blvd., Los Angeles 90046. (213) 874-3136.

October 1-December 17—**Cardiology.** UCLA. Wednesday evenings.

October 4-11—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

October 8—**Modern Therapy for Common Dermatologic Problems.** LLU. Wednesday. 4 hrs. $30.

October 10-11—**Mycology Review.** STAN. Friday-Saturday. A course for residents in dermatology and pathology. 14 hrs. Contact: Paul H. Jacobs, MD, Dermatology Dept., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

October 10-12—**Chest Disease Symposium.** The Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

October 11—**Allergy and Immunology in Office Practice.** PMC. Saturday. 6 hrs.

Ocober 13-17—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs. $290.

October 15-16—**Advanced Electrocardiography.** St. Francis Medical Center, Lynwood. Wednesday-Thursday. 12 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

October 18-25—**Cardiology.** USC at Mauna Kea Beach Hotel. Kamuela, Hawaii. One week. $325.

October 23-28—**Pacific Dermatologic Association.** Hilton Riviera, Palm Springs. Thursday-Tuesday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno, NV 89509. (702) 323-2461.

October 27-30—**Practical Electrocardiography Course for Primary Physicians.** Memorial Hospital Medical Center-UCI Center for Health Education at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: Center for Health Education. 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 29—**Endocrine Review.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Dept. of Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

October 30-November 1—**Cardiology Update 1980.** American College of Cardiology at Del Monte Hyatt, Monterey. Thursday-Saturday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 30-November 2—**California Society of Internal Medicine—Annual Meeting.** Doubletree Inn, Monterey. Thursday-Sunday. Contact: Carol Parlette, Exec. Dir., CSIM, 703 Market St., 1412 Central Tower, San Francisco 94103. (415) 362-1548.

November 1—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

November 5-8—**American Thyroid Association.** Holiday Inn at the Embarcadero, San Diego. Wednesday-Saturday. Contact: Dorothy Hickler, Exec. Sec., ATA, Univ. of MA Medical Ctr., 55 Lake Ave. N., Worcester, MA 01605. (617) 856-3115.

November 12—**Peptic Ulcer—Its Diagnosis and Treatment in the 1980's.** LLU. Wednesday. 4 hrs. $30.

November 13-15—**Allergy/Immunology for the Practicing Physician.** UCSF. Thursday-Saturday. 15 hrs. $150.

November 17-19—**International Symposium on Status Epilepticus.** UCLA at Miramar-Sheraton, Santa Monica. Monday-Wednesday. 20 hrs.

November 19-21—**Pediatric Cardiology.** USC at Palm Springs. Wednesday-Friday.

November 29-December 1—**Advances in Heart Disease 1981.** American College of Cardiology at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 1-3—**Cardiovascular-Pulmonary Update for the Practicing Physician.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 19 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

December 5—**Recognition and Management of Bleeding Disorders.** Children's Hospital Medical Center of Northern Calif. at Sir Francis Drake Hotel, San Francisco. Friday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

December 5-7—**Cardiac Rehabilitation.** International Medical Education Corp. at Wilshire Hyatt, Los Angeles. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

December 6-7—**Neurology for the Primary Care Physician.** UCLA. Saturday-Sunday.

December 10—**Collagen Disease—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $30.

OBSTETRICS AND GYNECOLOGY

August 23-28—**Practical Management of the Infertile Couple.** See Of Interest To All, August 23-28.

September 12-13—**Environmental Hazards During Pregnancy: A Clear and Present Danger.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs. $95.

September 25-27—**Advances in Obstetrics.** UCSF. Thursday-Saturday.

November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** UCSD at Bahia Hotel, San Diego. Wednesday-Friday. 19 hrs. $185. Contact: Ronald W. Coen, MD, UCSD Sch. of Med., C-019, La Jolla 92093. (714) 452-4424.

December 5-7—**5th Annual Symposium on Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort. Friday-Sunday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

PEDIATRICS

September 18-20—**Pediatric Urology.** UCD at Holiday Inn, Napa Valley. Thursday-Saturday. 12 hrs.

October 3-4—**Pediatric Topics: Neonatology.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs. $85.

October 8-9—**37th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: L.A. Pediatric Soc., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

October 25—**Hearing Impaired Child.** Peninsula Hospital, Burlingame. Saturday. Contact: Susan Norrell, c/o Radiology Dept., Peninsula Hosp., 1783 El Camino Real, Burlingame 94010. (415) 697-4061, ext. 479.

October 25-November 1—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education and L.A. Pediatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $200. Contact: Center for Health Education, MHMC, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 27-31—**4th Annual Pediatrics for the Practitioner—A Pediatric Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday. 21 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 1—**Pediatric Dermatology Seminar.** See Medicine, November 1.

November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** See Obstetrics-Gynecology, November 5-7.

November 19-21—**Pediatric Cardiology.** See Medicine, November 19-21.

November 21-24—**Pediatric Update.** American Academy of Pediatrics, Calif. Chapters 1, 2 and 3, at Hilton Hotel, Las Vegas. Friday-Monday. 15 hrs. $175, members; $200, nonmembers. Contact: AAP, Chap. 2, P. O. Box 2134, Inglewood 90305.

December 5-7—**Children and Their Skeletons: A Practical Approach.** UCD at Hyatt Del Monte, Monterey. Friday-Sunday.

PSYCHIATRY

August 15-20—**Neuropsychiatric Issues in the Law, Education and Medicine.** So. Calif. Neuropsychiatric Institute and Am. Psychiatric Assn. at Mauna Kea Beach Hotel, Kamuela, Hawaii. Friday-Wednesday. 14 hrs. Contact: Gail Waldron, MD, SCNPI, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

October 25—**Cognitive Prospectives in Psychiatry.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 14-16—**Infant Psychiatry III: Pathological Infants and Their Parents; Pathological Parents and Their Infants.** UCSF. Friday-Sunday.

November 17-21—**Group Therapy.** UCSF. Monday-Friday.

RADIOLOGY AND PATHOLOGY

September 1980-August 1981—**Current Surgical Pathology Practice.** Naval Regional Medical Center at Oak Knoll Naval Hospital, Oakland. Fridays; 7:45-9:00 a.m. Contact: R. W. Poley, Dept. of Pathology, Naval Regional Med. Ctr., Oakland 94627.

September 15-17—**3rd Annual Postgraduate Course in Medical Mycology (Dermatomycology).** See Medicine, September 15-17.

September 22-26—**Diagnostic Hematology.** American Society of Clinical Pathologists at Sheraton-San Diego Airport. Monday-Friday. 32½ hrs. $600, ASCP members; $700, Nonmembers. Contact: ASCP Educational Ctr., 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

September 27-October 4—**Diagnostic Radiology.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

October 10-11—**Mycology Review.** See Medicine, October 10-11.

October 10-12—**Society of Nuclear Medicine—5th Annual Western Regional Meeting.** Airport Marriott, Los Angeles. Friday-Sunday. Contact: SNM, P.O. Box 40279, San Francisco 94140. (415) 647-5909.

October 24-26—**Advances in Immunopathology.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Friday-Sunday. 17 hrs. $120. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

October 28-30—**Gram Negative Organisms: An Approach to Identification.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Thursday. 21 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 13-14—**Using the Clinical Lab.** UCLA. Saturday-Sunday.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

September 2-5—**IV International Symposium on Facial Nerve Surgery.** Ear Research Institute, Los Angeles. Tuesday-Friday. Contact: Facial Nerve Symposium, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

September 10—**Hematuria—An Approach to Diagnosis and Therapy.** LLU. Wednesday. 4 hrs. $30.

September 13-20—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 18-20—**Pediatric Urology.** See Pediatrics, September 18-20.

September 19-20—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

September 25-28—**Cost Effective Urological Diagnosis and Treatment.** Western Section, Am. Urological Assn. and AUA at Marriott's Rancho Las Palmas Resort, Palm Springs. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

September 26-27—**Vitrectomy.** UCSD at Vacation Village, San Diego. Friday-Saturday.

September 27—**Medical Malpractice in Ophthalmology. A Review of Common Diagnostic and Therapeutic Errors.** Estelle Doheny Eye Foundation, Los Angeles; Course coordinators Albert Tashma, MD and Ronald E. Smith, MD. Contact: Nancy Call, Estelle Doheny Eye Foundation, 1355 San Pablo Street, Los Angeles, CA 90033. (213) 224-7752.

September 28-October 2—**American Academy of Otolaryngology.** Convention Center, Anaheim. Sunday-Thursday. Contact: AAO, 15 Second St. SW, Rochester, MN 55901.

October 3-5—**State of the Art: Recent Advances in Head and Neck Surgery.** Institute for Medical Education and Research at Islandia Hyatt, San Diego. Friday-Sunday. 14 hrs. $200. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126 or (714) 294-5910.

October 9-11—**New Techniques in Hip Resurfacing and Replacement—In-depth Course and Workshop.** UCLA. Thursday-Saturday.

October 25-November 1—**Operative Arthroscopy.** UCLA at Maui, Hawaii. One week.

November 7-8—**Leg Amputations and Their Rehabilitation.** PMC at Hyatt on Union Square, San Francisco. Friday-Saturday. 12 hrs. $185.

November 14-15—**Vitrectomy/Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs. $450.

December 3-4—**Controversies and Update in Coronary Artery Bypass Surgery.** White Memorial Medical Center and LLU at Hilton, Los Angeles. Wednesday-Thursday. Contact: Dir. of Cont. Med. Ed., White Memorial Med Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000, ext 1460.

December 11-13—**Trauma.** No. Calif. Chap. of the Committee on Trauma of Am. College of Surgeons at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. Contact: Donald D. Trunkey, MD, Chief of Surgery, S.F. Gen. Hosp., 1001 Potrero Ave., San Francisco 94110.

December 12-13—**Ophthalmology Update.** UCD, UCSF, PMC, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

OF INTEREST TO ALL PHYSICIANS

August 16-17—**Parenteral and Enteral Nutrition—A Practitioner's Approach.** Memorial Hospital Medical Center, Long Beach. Saturday-Sunday. 10 hrs. Contact: Clinical Nutrition Dept., Memorial Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801 (213) 595-2231.

August 16-27—**23rd Annual Hawaii Refresher Course.** USC at Sheraton-Waikiki Hotel, Maui. 12 days. 39 hrs. $350.

August 17-18—**Computers in Medicine—Applications of Artificial Intelligence Techniques.** STAN. Sunday-Monday. 11½ hrs. $40. Contact: William J. Clancey, AIM Tutorial Coordinator, Rm. TC 117, Div. of Gen. Int. Med., Stanford Univ. Sch. of Med., Stanford 94305.

August 17-22—**Advanced Diving Medicine.** UCSF. Sunday-Friday.

August 23-28—**Practical Management of the Infertile Couple—4th Annual Edward Tyler Symposium.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. Saturday-Thursday. 16 hrs. $225. Contact: Jetset Tours, 2029 Century Park East, Suite 2130, Los Angeles 90067.

August 24-29—**Family Practice Refresher Course—8th Annual.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

September 6—**Drug Abuse.** UCLA. Saturday.

September 8-19—**Intensive Residency in Occupatioual Medicine, Session I.** UCSF. Two weeks.

September 10—**Alcoholism.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

September 10—**Sexually Transmitted Hepatitis: The Facts of Life.** See Medicine, September 10.

September 22-26—**Primary Care: Current Management of Common Office Problems.** UCSF. Monday-Friday.

September 24-27—**Society for Computer Medicine.** Hilton, San Diego. Wednesday-Saturday. Contact: SCM, 1901 N. Ft. Myer Dr., Ste. 602, Arlington, VA 22209.

September 24-28—**Human Dimensions in Medicine.** UCSD at Vacation Village, San Diego. Wednesday-Sunday.

September 25—**Venereal Disease.** Calif. Venereal Disease Controllers' Assn. and CMA at Tiburon Lodge, Tiburon. Thursday. Contact: Manuel De Pinna, CMA.

September 25-December 4—**Recent Advances in Alcoholism: Biological and Behavioral Effects.** UCI. Thursdays; 7:00-10:00 p.m. 30 hrs. Contact: UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

September 26—**Preparing the Chronically Ill Patient for "Going Home."** Mt. Zion Hospital and Medical Center at St. Mary's Cathedral, San Francisco. Friday. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

September 26-27—**Introduction to Microcomputers.** PMC at Lone Mountain Campus-USF. Friday-Saturday. 12 hrs. $395.

September 29-October 1—**Alcoholism and Chemical Dependency Treatment—Where Do We Go From Here?** Scripps Memorial Hosp. at Vacation Village, San Diego. Monday-Wednesday. 15 hrs. $175. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110.

October 3-4—**Medicine in the 80's—State of the Art.** Unity Church of Hawaii, Hawaii Medical Assn., Univ. of Hawaii at Prince Kuhio Hotel, Honolulu. Friday-Saturday. 7 hrs. Contact: Unity Church of Hawaii, 3608 Diamond Head Circle, Honolulu 96815. (808) 735-4436.

October 10-11—**Acute Care and Critical Care in Medicine.** Southern Calif. Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

October 11—**Ophthalmology for the Family Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

October 11-12—**The Healing Brain II.** UCSF at Sheraton Palace, San Francisco. Saturday-Sunday. $95. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

October 13-16—**Fifth Annual Family Practice Update.** LLU. Monday-Thursday. 31 hrs. $200.

October 13-17—**Hawaii Medical Association—124th Annual Meeting.** Pacific Beach Hotel, Waikiki. Monday-Friday. Contact: HMA, 320 Ward Ave., Ste. 200, Honolulu 96814. (808) 536-7702.

October 15-18—**24th Annual Western Occupational Health Conference.** Western Occupational Med. Assn. at Hotel del Coronado, Coronado. Wednesday-Saturday. Contact: Joe Donovan, WOHC, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 16-18—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 17-19—**Nutrition for the Practicing Physician.** UCSF. Friday-Sunday.

October 24—**Patient Care—Challenging the Image.** St. Francis Medical Center at Sheraton Hotel, Anaheim. Friday. 7 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

October 24-25—**Geriatric Medicine Today.** Western Div., Am. Geriatrics Soc., at Hyatt Regency, San Francisco. Friday-Saturday. Contact: AGS, Western Div., 13220 105th Ave., Bldg. B, Rm. 61, Sun City, AZ 85351.

October 24-26—**In Pursuit of Wellness.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday. Contact:

Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

October 25-26—**Eight Common Problems.** UCLA. Saturday-Sunday.

October 28-31—**American Academy of Occupational Medicine.** Hyatt Regency, San Francisco. Tuesday-Friday. Contact: AAOM, 150 N. Wacker Dr., Chicago 60606.

October 30-November 1—**Postgraduate Institute on Nutrition.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

November 2-5—**California Academy of Family Physicians—Annual Scientific Assembly.** Disneyland Hotel, Anaheim. Sunday-Wednesday. Contact: William W. Rogers, Exec. Sec., CAFP, 9 First St., Rm. 900, San Francisco 94105. (415) 982-6091.

November 3-7—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $275.

November 3-7—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $290.

November 5—**Sexuality.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Medical Center, 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

November 7-8—**Psychiatry for the Primary Care Physician.** UCD. Friday-Saturday.

November 8-9—**Cross Cultural and Trans Cultural Issues in Family Health Care.** UCSF. Saturday-Sunday. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

November 13-15—**Biofeedback and Family Practice.** UCLA and Biofeedback Society at San Jose. Friday-Saturday. Contact: UCLA.

November 13-15—**Medical Aspects of Products Liability.** UCSF. Thursday-Saturday.

November 15—**Criteria for Evaluating Pseudoscience, Cults and Holistic Medicine.** San Jose State University. Saturday. 8 hrs. $40. Contact: Susan M. Grube, MPH, Cont. Ed., San Jose State Univ., Washington Sq., San Jose 95192. (408) 277-3778.

November 15-16—**Fourth Annual National Symposium on Aging.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

November 16—**Frontiers in Medicine—12th Annual Symposium.** UCLA and Granada Hills Community Hospital at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344.

November 21-23—**Sports Medicine: The Physician and the Injured Athlete.** UCD at Marriott Inn, Berkeley. Friday-Sunday. 12 hrs.

November 21-25—**Gerontological Society—Annual Scientific Meeting.** Town and Country Hotel, San Diego. Friday-Tuesday. Contact: Dr. Eugene J. Towbin, VA Hospital, Little Rock, AR 72206.

December 4—**Nutrition and Aging.** STAN. Thursday. 7 hrs.

December 5-7—**Human Sexuality.** Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

December 13—**Diagnosis and Treatment of Sleep Disorders Patients.** STAN at Marriott, Santa Clara. Saturday. 7 hrs. $35.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

(Continued on Page 25)

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ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

MONTANA

October 2-4—**Montana Medical Association Annual Meeting.** Thursday-Saturday. Bozeman. Contact: Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

IDAHO

August 22—**Intermountain Infectious Disease Symposium.** Idaho Falls. Friday. Intermountain Experience Center. Contact: DeVon Hale, MD, P.O. Box 1602, Idaho Falls, ID 83401. (208) 529-0072.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

MEDICINE

September 5-6—**Current Perspectives on Rheumatology.** Ashland, Friday-Saturday. Ashland Hills Inn. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

November 13-14—**Symposium on Critical Care Medicine.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 23-25—**Northwest Review of Obstetrics & Gynecology.** Portland, Thursday-Saturday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

PSYCHIATRY

September 13—**Movement Disorders.** Portland, Saturday. OMA Headquarters, 5210 SW Corbett Ave., Portland, OR 97201. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

September 18-19—**Dermatology for the Non-Dermatologist.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

September 26—**Shaw Memorial Lectures on Geriatric Medicine.** Portland, Friday. Oregon Medical Association Building. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

October 3-4—**Washington State Medical Association Annual Meeting Scientific Program.** Vancouver, WA/Portland, OR. Friday-Saturday. Thunderbird-Jantzen Beach. Contact: Mrs. Marcia Wahlman, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA 98121. (206) 623-4801.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

August 21-22—**Current Concepts in Neonatal and Perinatal Medicine.** Seattle. Monday-Tuesday. Health Sciences Auditorium, U/W School of Medicine, Div. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

September 5-6—**Advances in Clinical Microbiology.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W School of Medicine, Dept. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

September 9-11—**Noninvasive Diagnostic Techniques.** Seattle. Tuesday-Thursday. U/W Health Sciences Building. Contact: U/W School of Medicine, Dept. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

September 11-12—**Arthritis Days.** Seattle. Thursday-Friday. Hilton Hotel. Contact: Pamela Lindquist, Western Washington Chapter, Arthritis Foundation, 710 Second Ave., Seattle, WA 98104. (206) 622-2481.

September 12—**Permanent Cardiac Pacing.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W School of Medicine, Dept. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

September 18-20—**Plastic Surgery for Primary MDs.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W School of Medicine, Dept. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

September 19-20—**Spokane Developmental Disorders in Children.** Spokane. Friday-Saturday. Sacred Heart Hospital. Contact: U/W School of Medicine, Dept. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

September 21-23—**Emergency Medicine in Office Practice.** Walla Walla. Sunday-Tuesday. Walla Walla General Hospital. Contact: Max W. Hammonds, MD, Director, Continuing Medical Education, Walla Walla General Hospital, 1025 South Second Avenue, P.O. Box 1398, Walla Walla, WA 99362. (509) 525-0480.

September 22-26—**Advances in Family Practice.** Seattle. Monday-Friday. U/W Health Sciences Buliding. Contact: U/W School of Medicine, Dept. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

September 25-28—**The Spine, Advances in Practical Management.** Seattle. Thursday-Sunday. Olympic Hotel. Contact: U/W School of Medicine, Div. of CME SC-50, Seattle, WA 98195. (206) 543-1050.

September 27—**Annual Cancer Symposium: Current Concepts in Gynecological Malignancies.** Tacoma. Saturday. Tacoma General Hospital. Contact: Karen Tilley, Department of Oncology, Tacoma General Hospital, 315 South K Street, Tacoma, WA 98405. (206) 597-6964.

October 3-4—**Washington State Medical Association Annual Meeting Scientific Program.** Vancouver, WA/Portland, OR. Friday-Saturday. Thunderbird-Jantzen Beach. Contact: Mrs. Marcia Wahlman, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA 98121. (206) 623-4801.

November 6-9—**United States Section, International College of Surgeons Annual Meeting.** Las Vegas, NV. Thursday-Sunday. Aladdin Hotel. Contact: Franklin R. Smith, MD, 942 Medical & Dental Bldg., Seattle, WA 98101. (206) 682-1944.

November 13-15—**Street Drugs.** Seattle. Thursday-Saturday. Park Hilton Hotel. Contact: Marilyn Carlson, Northwest Hospital Education & Training Dept., 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ex. 686.

November 13-15—**Topics in Emergency Medicine.** Seattle. Thursday-Saturday. Seattle Hyatt House (Sea-Tac). Contact: Joan Palmer, c/o WSHA, 419 Occidental Avenue South, Seattle, WA 98104. (206) 624-7240.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

August 26-28
SPONSOR: VA Regional Medical Education Center
TITLE: **Conflict, Confrontation, and Stress**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Alan Lundgren (801) 582-1565, Ext. 1100

September 11
SPONSOR: Rocky Mountain Center for Occupational and Environmental Health
TITLE: **Occupational Health for the 1980's**
LOCATION: Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

September 11-12
SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ the Utah State Medical Association
TITLE: **40th Annual AMA Congress on Occupational Health**
LOCATION: Salt Lake Hilton
FEE: $65.00—physicians
$45.00—allied health professionals
CREDIT: 12 hours
CONTACT: Katharine C. Blosch (801) 581-5718

(Continued on Page 29)

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Carbon Hospital, Washington Park, Price 84501. (801) 637-1123
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84107 (801) 262-3461
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UU: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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September 12
SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Medical Management of Ischemic Heart Disease**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: 3 hours
CONTACT: Stan Everett (801) 350-1004

September 18-20
SPONSOR: University of Utah
TITLE: **Preceptor Teaching Skills**
LOCATION: Snowbird, Utah
FEE: $15.00
CREDIT: 10.5 hours
CONTACT: Donna Harris (801) 581-8250

September 22-25
SPONSOR: VA Regional Medical Education Center
TITLE: **Sexual Health**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: George Keiser, PhD (801) 582-1565, Ext. 1100

September 30-October 3
SPONSOR: University of Utah
TITLE: **Utah State Medical Association Scientific Meeting**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: Up to 12 hours
CONTACT: Maxcine Fry (801) 355-7477

October 1-2
SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

October 10-11
SPONSOR: University of Utah/The Upjohn Company
TITLE: **2nd Fall Arthritis Conference—Rheumatology: Clinical Assessment for the Practicing Physician**
LOCATION: Park City, Utah
FEE: $70.00
CREDIT: 11 hours
CONTACT: Mark Mueller, MD (801) 581-7724

October 16
SPONSOR: LDS Hospital (with Intermountain Thoracic Society, Utah Heart Association and University of Utah)
TITLE: **Postgraduate Course—Pulmonary Heart Disease**
LOCATION: LDSH
FEE: To be announced
CREDIT: 6 hours
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

November 6
SPONSOR: LDS Hospital
TITLE: **Pulmonary Heart Disease**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

December 12
SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Hypertension**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

January 24-31
SPONSOR: University of Utah
TITLE: **6th Annual Snowbird Radiology Conference**
LOCATION: Snowbird
FEE: To be announced
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8188

January 31-February 7
SPONSOR: University of California, San Francisco, CA
TITLE: **Infectious Diseases in Clinical Practice**
LOCATION: Park City, Utah
FEE: $200.00 ($250.00 after October 15, 1980)
CREDIT: 20 hours
CONTACT: Extended Programs in Medical Education
University of California
1308 3rd Avenue
San Francisco, CA 94143
(415) 666-2483 or 666-2894

February 9-12
SPONSOR: University of Utah
TITLE: **10th Annual Family Practice Refresher Course**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 28 hours
CONTACT: David N. Sundwall, MD (801) 581-8633

February 15-20
SPONSOR: University of Utah
TITLE: **Update on Clinical Microbiology and Immunology**
LOCATION: Park City
FEE: To be announced
CREDIT: 24 hours
CONTACT: John M. Matsen, MD (801) 581-5514

February 20-24
SPONSOR: University of Utah
TITLE: **26th Annual Postgrad Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: 16 hours
CONTACT: Theodore H. Stanley, MD (801) 581-6393

February 21-24
SPONSOR: University of Utah
TITLE: **OB-GYN 22nd Annual Postgrad Course**
LOCATION: Park City
FEE: To be announced
CREDIT: 16.5 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-27
SPONSOR: University of Utah/Intermountain Pediatric Society/American Academy of Pediatrics
TITLE: **Common Problems in Pediatrics III**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 16 hours
CONTACT: Bruce Buehler, MD (801) 581-7877

February 25-28
SPONSOR: University of Utah
TITLE: **Gynecologic Oncology Course**
LOCATION: To be announced
FEE: To be announced
CREDIT: 16.5 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-March 7
SPONSOR: University of Utah
TITLE: **Midwinter Radiology Pacific Cruise Meeting**
LOCATION: Departs from Los Angeles
FEE: $300.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

February 28-March 7
SPONSOR: University of Utah
TITLE: **6th Annual Advances in Internal Medicine**
LOCATION: Snowbird
FEE: $225.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1981—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 22-26, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 24-27, 1980, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 13-17, 1980, Pacific Beach Hotel, Waikiki.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1981—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Convention: November 7-8, 1980, Kachina Lodge, Taos.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 30-October 3, 1980, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA/Portland, OR.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Ramada Snow King Inn, Jackson.

February 28-March 7

SPONSOR: University of Utah
TITLE: **Nutrition and Contemporary Medicine**
LOCATION: Park City
FEE: $200.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 7-14

SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 14-21

SPONSOR: University of Utah
TITLE: **3rd Annual Park City Radiology Conference: Neuroradiology**
LOCATION: Park City
FEE: $240.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

April 8-10

SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ University of Arizona Center for Occupational Safety and Health/University of Texas Health Science Center, School of Public Health
TITLE: **3rd Annual Park City Environmental Health Conference: Legal and Ethical Dilemmas in Occupational Health**
LOCATION: Prospector Square Lodge, Park City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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Librium®

chlordiazepoxide HCl/Roche

- ☐ Proven antianxiety performance
- ☐ An unsurpassed safety record
- ☐ Predictable patient response
- ☐ Minimal effect on mental acuity at recommended doses
- ☐ Minimal interference with many primary medications, such as antacids, anticholinergics, diuretics, cardiac glycosides and antihypertensive agents

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. Oral—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) Capsules, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Libritabs® (chlordiazepoxide) Tablets, 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable.

synonymous with relief of anxiety

ROCHE

Roche Products Inc.
Manati, Puerto Rico 00701

Please see following page.

Librium® CIV

chlordiazepoxide HCl/Roche

5 mg, 10 mg, 25 mg capsules

synonymous with relief of anxiety

ROCHE

Please see preceding page for a summary of product informatio

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THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON JUN 9 1981

THE WESTERN Journal of Medicine

VOLUME 133 • NUMBER 3 **SEPTEMBER 1980**

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★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA, MONTANA AND IDAHO; OREGON; WASHINGTON; UTAH**
(See Advertising Page 35)

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the Utah State Medical Association and the Washington State Medical Association**

The stress-secretion relationship in duodenal ulcer*

The best available evidence suggests that anxiety and emotional tension stimulate acid-pepsin secretion.[1] Also, the development of an ulcer crater in predisposed individuals, or the aggravation of ulcer symptoms, is often typically preceded by a stressful event or situation. *Anxiety* in particular seems to play a determining role in the course and prognosis of the disease, as well as its etiology.

A psychobiologic treatment

To obtain comprehensive relief, many duodenal ulcer patients need more than specific, acid-inhibiting medication—they also need dependable reduction of associated anxiety and emotional tension. With adjunctive Librax you can conveniently give your patient *both* clinical benefits from a single medication.

The pituitary gland plays a key role in the neurohormonal response to emotional stress, leading to an increase in gastric secretion.[2]

1. Isenberg J, Richardson CT, Fordtran J: Pathogenesis of peptic ulcer, chap. 46, in *Gastrointestinal Disease*, ed. 2, edited by Sleisenger MH, Fordtran JS. Philadelphia: W.B. Saunders Company, 1978, vol. 1, pp. 800, 801.
2. Sun DCH: Etiology and pathology of peptic ulcer, chap. 27, in *Gastroenterology*, edited by Bockus HL, *et al*. Philadelphia: W.B. Saunders Company, 1974, pp. 57

ROCHE

*Librax has been evaluated as possibly effective for this indication.

Please see brief summary of prescribing information on last page of this advertisement.

More than an antisecretory agent... acts on the entire disease entity

Adjunctive

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

antianxiety
antisecretory
antispasmodic

The duodenal ulcer reflects the erosion of a vulnerable mucosa by acid-pepsin secretion.[2]

CIS A. COUNTWAY
OF MEDICINE
STON
9 1981

When your duodenal ulcer* patient needs more than an antisecretory agent...

Adjunctive Librax®

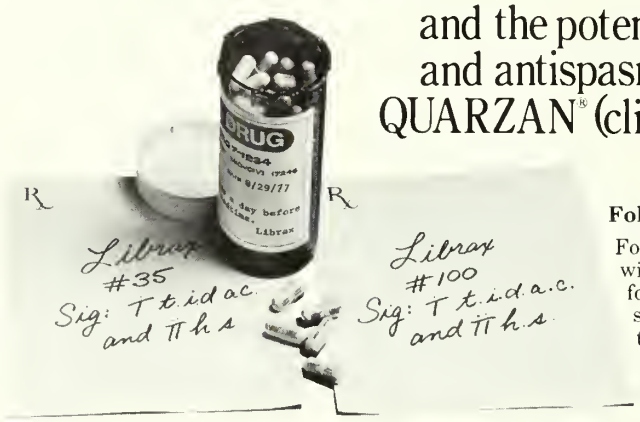
Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

The only duodenal ulcer therapy that provides the specific antianxiety action of LIBRIUM® (chlordiazepoxide HCl/Roche)

and the potent antisecretory and antispasmodic actions of QUARZAN® (clidinium Br/Roche)

Initial Rx

The initial prescription allows evaluation of patient response to therapy.



Follow-up Rx

Follow-up therapy with a prescription for a 2- to 3-week supply of medication usually helps maintain patient gains.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl/Roche) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment, blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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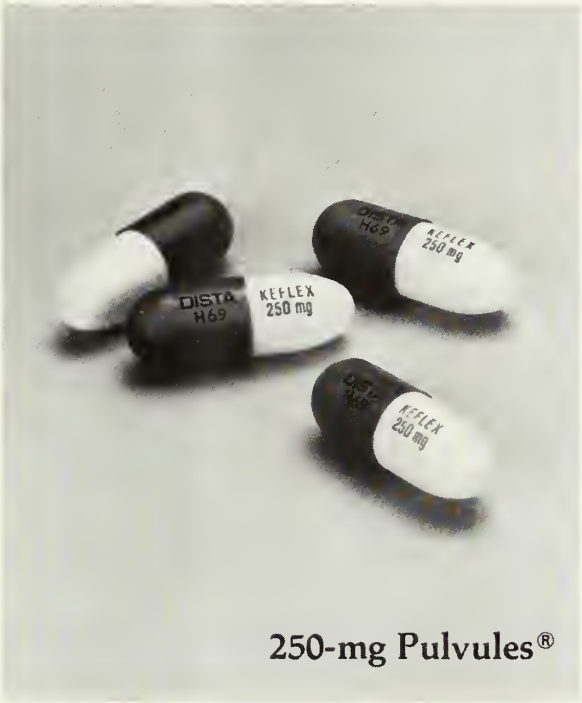

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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section)

Complete literature available on request from Professional Services Dept. PML.

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*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

[1] Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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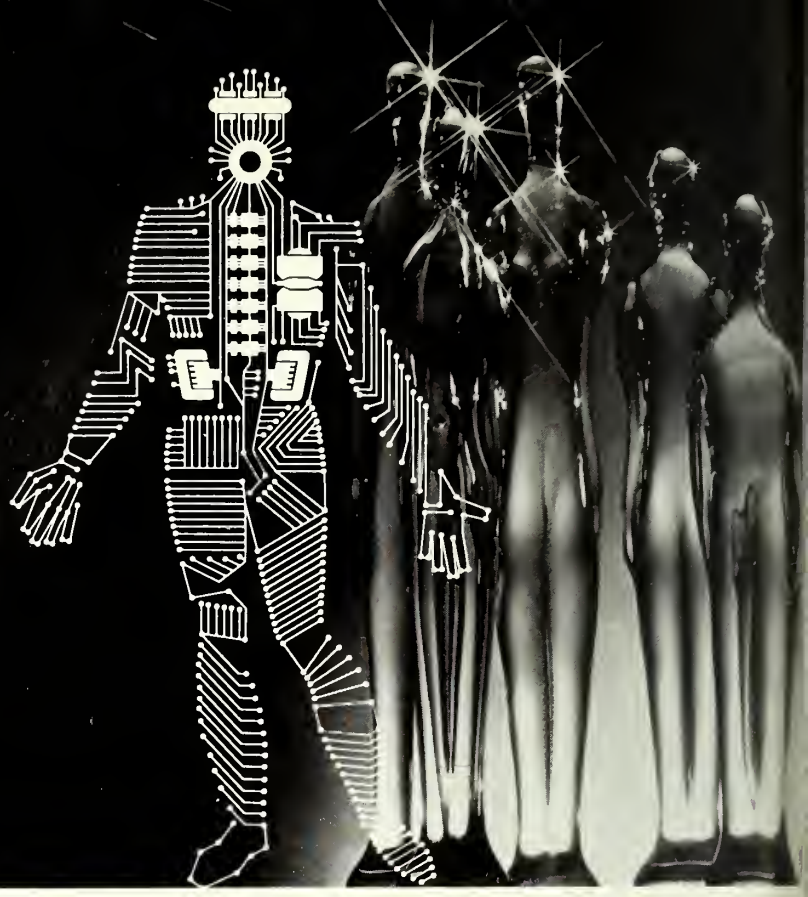

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Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

The usual starting dose of Catapres is 0.1 mg at brea fast and 0.1 mg at bedtime. Some patients may bene from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

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Tablets of 0.1, 0.2, 0.3 mg

Indication: The drug is indicated in the treatment of hypertension. As an anti-hypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 mo longer.

Adverse Reactions: The most common reactions are dry mouth, drowsine sedation. Constipation, dizziness, headache, and fatigue have been re Generally these effects tend to diminish with continued therapy. The fo reactions have been associated with the drug, some of them rarely. (In instances an exact causal relationship has not been established.) These i Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnorma liver function tests; one report of possible drug-induced hepatitis without and hyperbilirubinemia in a patient receiving clonidine hydrochloride thalidone and papaverine hydrochloride. Weight gain, transient elevation glucose, or serum creatine phosphokinase: congestive heart failure, Ra phenomenon; vivid dreams or nightmares, insomnia, other behavioral cl nervousness, restlessness, anxiety and mental depression. Also ra gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not ass with a rash, impotence, urinary retention, increased sensitivity to alcohol, c itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecc weakly positive Coombs' test, asymptomatic electrocardiographic abnor manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminishe sent reflexes and vomiting followed the accidental ingestion of Catapres (c hydrochloride) by several children from 19 months to 5 years of age. lavage and administration of an analeptic and vasopressor led to comp covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30 intervals usually abolishes all effects of Catapres, (clonidine hydrochlorid dosage.

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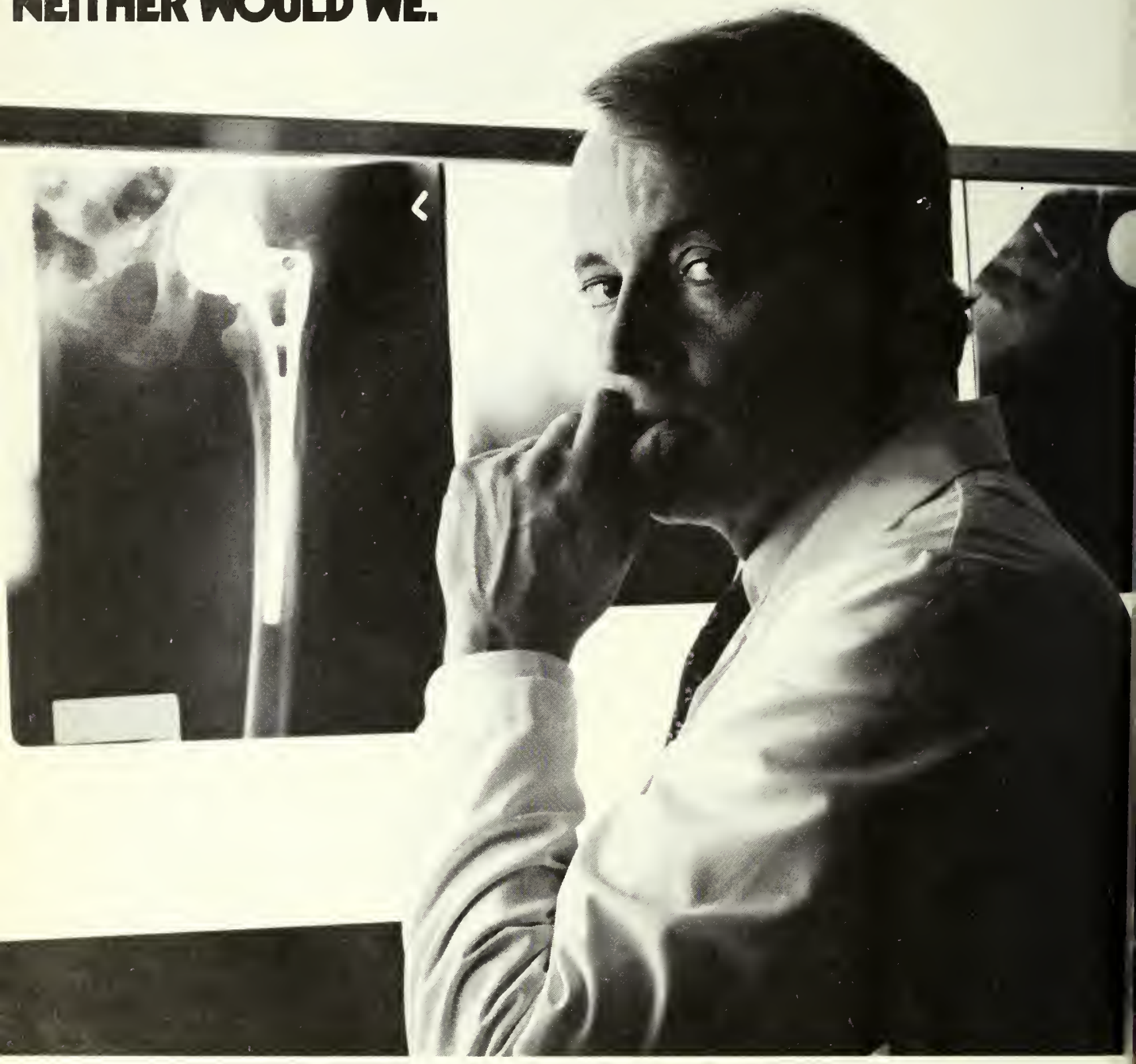

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

HUMAN NUTRITION AND DIETETICS—Seventh Edition—Sir Stanley Davidson, BA Cantab, MD, FRCP Edin, FRCP Lond, MD (Hon Oslo), LL D Edin and Aberd, Extra Physician to Her Majesty The Queen in Scotland; Reg Passmore, DM Oxon, FRCP Edin, Reader in Physiology, University of Edinburgh; John F. Brock, DM Oxon, FRCP Lond, DSc (Hon Natal), FACP (Hon), FCP (Hon SA), Emeritus Professor of Medicine, University of Cape Town; Honorary Consulting Physician, Groote Schuur Hospital; and A. Stewart Truswell, MD Cape Town, FRCP Lond, FFCM, Boden Professor of Human Nutrition, Sydney University, Australia, Head of Nutrition Section School of Public Health and Tropical Medicine, Sydney, Honorary Consultant in Nutrition, Royal Prince Alfred Hospital, Sydney. Churchill Livingstone Inc., 19 West 44th Street, New York, NY (10036), 1979. 641 pages, no price given.

INFECTIOUS DISEASES—Focus on Clinical Diagnosis—Edited by Haragopal Thadepalli, MD, Chief, Division of Infectious Diseases, Martin Luther King, Jr., General Hospital; Associate Professor of Medicine, Charles R. Drew Postgraduate School of Medicine, University of Southern California School of Medicine, Los Angeles. Medical Examination Publishing Co., Inc., 969 Stewart Ave., Garden City, NY (11530), 1980. 848 pages, $23.50 (paperback).

MANUAL OF ULTRASONOGRAPHY—Kenneth J. W. Taylor, MD, PhD, FACP, Professor of Radiology, Department of Diagnostic Radiology; Paula Jacobson, RT, RDMS, Diagnostic Sonographer, Department of Diagnostic Radiology; Carol A. Talmont, RT, RDMS, Diagnostic Sonographer, Department of Diagnostic Radiology, and Ralph Winters, RT, RDMS, Diagnostic Sonographer, Department of Diagnostic Radiology, Yale-New Haven Hospital, New Haven, Connecticut; drawings by Caroline R. Taylor, MD. Churchill Livingstone Inc., 19 West 44th Street, New York City (10036), 1980, 211 pages.

NUTRITION AND VITAMIN THERAPY—Michael Lesser, MD, psychiatrist in private practice in Berkeley, California. Grove Press, Inc., 196 W. Houston St., New York City (10014), 1980. 240 pages, $7.95 (paperback).

PEDIATRIC GASTROENTEROLOGY—Case Studies—William Liebman, MD, Assistant Professor of Pediatrics, Pediatric Gastroenterology Unit, University of California, San Francisco, School of Medicine. Medical Examination Publishing Co., Inc., 969 Stewart Avenue, Garden City, NY (11530), 1980. 496 pages, $18.00 (paperback).

THE PRINCIPLES OF PHYSIOLOGY—Second Edition—David Jensen, PhD, Denver, Colorado. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1980. 1,068 pages, $29.50.

PROMETHEAN ETHICS: Living With Death, Competition, and Triage—Garrett Hardin, PhD, formerly Professor of Biology and Human Ecology, University of California, Santa Barbara. University of Washington Press, Seattle, WA (98105), 1980. 82 pages, $7.95.

A PSYCHIATRIC GLOSSARY—5th Edition—American Psychiatric Association, 1980—Edited by a Subcommittee of the Joint Commission on Public Affairs, Arnold Werner, MD, Chairman, Robert J. Campbell, MD, Shervert H. Frazier, MD, and Evelyn M. Stone, and Jane Edgerton, MA, APA Staff. American Psychiatric Association, 1700 - 18th Street, NW, Washington, DC (20009), 1980. 142 pages, $5.95 each, 10-24 copies, $5.35 each; 25-99, $5.00; 100 or more, $4.75 (paperback).

RECENT ADVANCES IN GASTROENTEROLOGY—Number Four—Edited by Ian A. D. Bouchier, MD, FRCP (Lond), FRCP (Edin), Professor of Medicine, University of Dundee, Ninewell Hospital and Medical School, Dundee. Churchill Livingstone Inc., 19 West 44th St., New York City (10036), 1980, 347 pages, no price given.

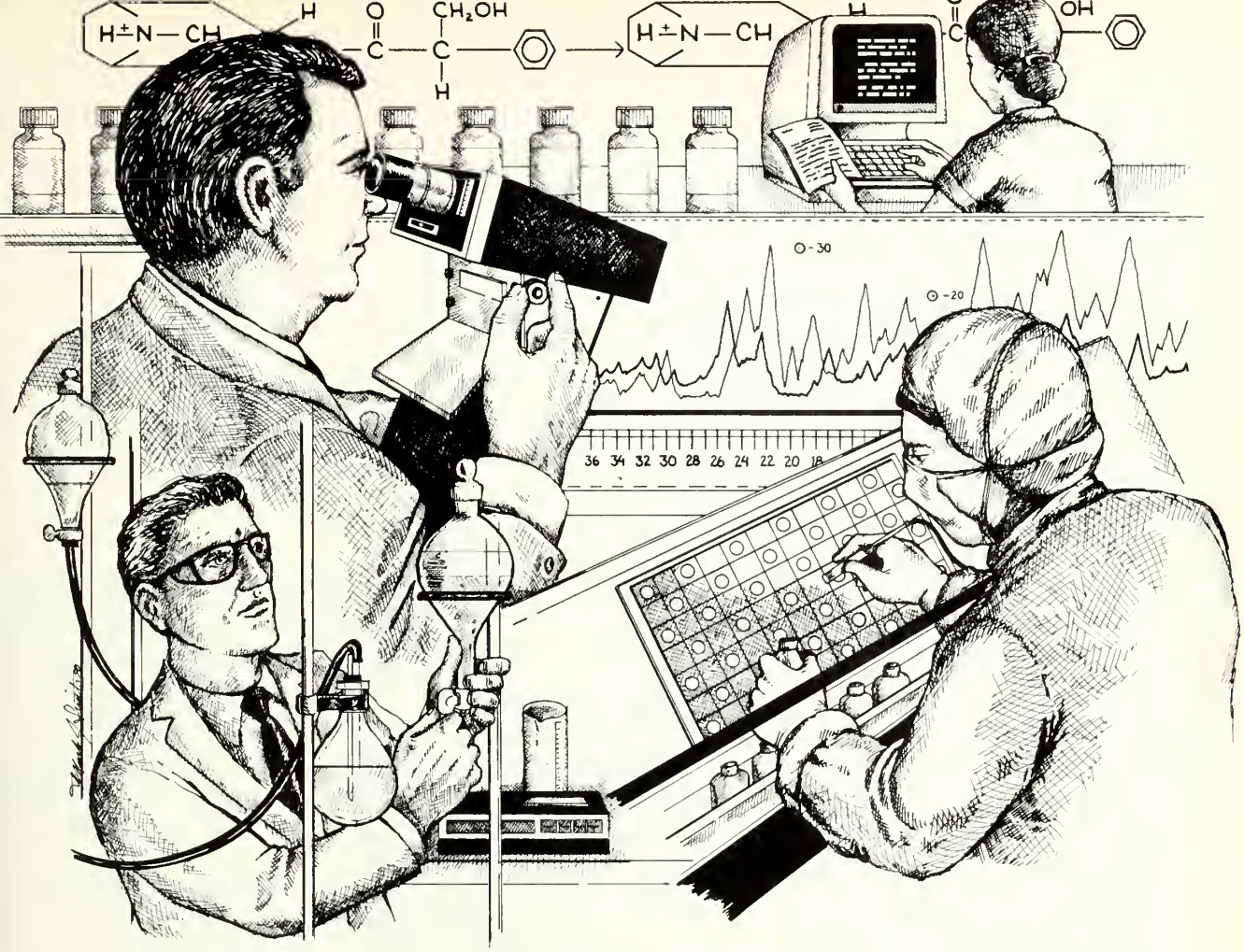
REVIEW OF MEDICAL MICROBIOLOGY—Fourteenth Edition—Ernest Jawetz, PhD, MD, Professor of Microbiology and Medicine, Lecturer in Pediatrics, University of California, San Francisco; Joseph L. Melnick, PhD, Distinguished Service Professor of Virology and Epidemiology, Baylor College of Medicine, Houston; and Edward A. Adelberg, PhD, Professor of Human Genetics, Yale University School of Medicine, New Haven. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 593 pages, $14.00.

SHOCK-TRAUMA—Jon Franklin and Alan Doelp. St. Martin's Press, 175 Fifth Avenue, New York City (10010), 1980. 246 pages, $9.59.

SPORTS MEDICINE FOR THE ATHLETIC FEMALE—Edited by Christine E. Haycock, MD, Associate Professor of Surgery, New Jersey Medical School, Newark. Medical Economics Books (2120-DPRDO), Box 157, Florence, KY (41042), 1980. 412 pages, $27.50, plus $1 handling (price subject to change).

STRESS IN HOSPITAL—Patients' Psychological Reactions to Illness and Health Care—Jenifer Wilson-Barnett, BA, MSc, PhD, SRN, DipN, Lecturer in Nursing Studies, Chelsea College, University of London. Churchill-Livingston, Edinburgh, distributed in the USA by Longman Inc., 19 West 44th Street, New York City (10036), 1979. 124 pages (paperback), no price given.

SUNNYHILL—The Health Story of the 80's—Bruce and Barbara Small. Small and Associates, Publishers, R.R. #1, Goodwood, Ontario, Canada L0C 1A0, 1980. 208 pages, $12.95 US/$14.95 CAN plus $1 postage.



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Refer to: Cook DM: Pituitary tumors—Current concepts of diagnosis and therapy. West J Med 133:189-196, Sep 1980

Pituitary Tumors—Current Concepts of Diagnosis and Therapy

DAVID M. COOK, MD, *Portland, Oregon*

Familiarity with the concepts and methods of diagnosis and their limitations is essential to outline a plan of investigation for individual patients suspected of having pituitary tumors. Therapy depends somewhat on the extent of suprasellar extension, a factor which especially limits irradiation. The role of transsphenoidal and other forms of pituitary operations must await long-term follow-up. This is especially true because we do not know the role of the hypothalamus in the pathogenesis of pituitary tumors.

PITUITARY TUMORS no longer can be looked on as a rare medical curiosity. It is estimated that asymptomatic pituitary tumors are present in 25 percent of all pituitary glands.[1,2] The distribution seems to have a two-to-one male predominance, based on autopsy studies.[1] The care of patients with pituitary tumors covers many medical disciplines. Endocrinologists play a major role in determining hormonal aspects and neuro-ophthalmologists in defining the degree of optic nerve damage. Neuroradiologists are important in diagnosis because in many cases no hormonal or ophthalmologic derangements can be identified.[3] Either a neurosurgeon or a radiation therapist (or both) is instrumental in definitive treatment and a primary care physician often is involved in treating the patient for long-term pituitary deficiencies after initial therapy.

How can tumors be harmful? As indicated in Table 1 there are two major mechanisms by which pituitary tumors can cause morbidity: (1) mass lesion effects and (2) hormonal effects. Below, we will review methods used to diagnose mass lesion and hormonal effects of pituitary tumors. Special emphasis will be placed on the limitations and specificity of these procedures.

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Submitted, revised, January 31, 1980.

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Methods to Evaluate Mass Lesion Effects

Visual Field Testing

Pituitary tumors can cause visual defects by exerting pressure on the optic nerves. A variety of field defects can be observed with pituitary tumors in addition to the classic bitemporal hemianopsia.[4]

Various methods have been used to examine visual fields to confirm optic nerve compression (Table 2). The list in Table 2 is incomplete, but provides the most common methods available. Confrontation and "red desaturation" examinations can be done by any clinician, whereas tangent screen examination and Goldmann perimetry require special equipment. Confrontation field examination is not as sensitive as other methods. In a study of 27 patients with pituitary tumors,[3] visual field defects in four patients were missed by confrontation but detected by tangent screen examinations. In approximately 80 percent of cases the optic chiasm is located over the center of the posterior two thirds of the sella, in 12 percent it is located directly over the center of

ABBREVIATIONS USED IN TEXT
ACTH = adrenocorticotropic hormone
CSF = cerebrospinal fluid
FSH = follicle-stimulating hormone
HGH = human growth hormone
LH = luteinizing hormone
TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone

the sella and in 4 percent it is found anteriorly.[5] The chiasm is therefore in a vulnerable position to be trapped by an enlarging pituitary tumor. Because the lower fibers in the chiasm contain mainly crossing fibers from the lower nasal retinal quadrants (that is, those serving the upper temporal visual quadrants), the function of these lower fibers is often the first to be interrupted by a tumor compressing the inferior surface of the chiasm. This interruption results in a peripheral bitemporal hemianopsia of the upper quadrant. The decussating central retinal fibers cross in the posterior part of the chiasm and form a bundle called the papulomacular bundle. Scotomatous hemianopsia is due to compression of these decussating fibers. Loss of central color vision is often the earliest finding when the papulomacular bundle is compressed by a pituitary tumor.

TABLE 1.—*Major Mechanisms of Morbidity Caused by Pituitary Tumors*

Mass Lesion Effects
- Visual field defects
- CSF rhinorrhea (erosion into sphenoid sinus)
- Hydrocephalus (compress aqueduct of Silvius)
- Headaches

Hormonal Effects
- Excess hormone syndromes such as acromegaly or Cushing syndrome
- Deficiency of one or more hormones by compression (?reversible)
- Excess of one hormone causing deficiency of second (example: prolactin excess→gonadotropin deficient)

CSF = cerebrospinal fluid

TABLE 2.—*Common Methods of Examining Visual Fields in Patients Suspected of Having a Pituitary Tumor*

Method	*Requires Special Equipment*
Confrontation	No
"Red desaturation"	No
Tangent screen	Yes
Goldmann perimetry	Yes

TABLE 3.—*Diagnostic Accuracy of Various Radiologic and Visual Field Tests Done at the University of Oregon Health Sciences Center (1968-1978)*

Study	*No. of Procedures*	*No. Positive*
Plain skull films	55	45
Size	55	31
Double floor	55	15
Erosion	55	30
Sellar tomograms	20	19
Pneumoencephalogram	45	28
Angiogram	26	15
CT scan	9	3
Visual fields	55	19

CT = computerized tomographic (scan)

Wilson and Falconer[6] found loss of central vision in 48 percent of patients (24 of 50) with pituitary tumors compared with 36 percent with the more classic bitemporal hemianopsia. Chiasmal compression by a pituitary tumor is seldom observed without loss of central color vision (verbal communication with Dr. William T. Shults, Associate Professor, Neuro-ophthalmology, University of Oregon, Health Sciences Center, December 1979), which can be detected in a physician's office using the red desaturation test for central color vision.

Visual field defects caused by pituitary tumors are seldom produced without radiologic abnormalities. Slight alteration of visual fields caused by these tumors in nearly all cases have been accompanied by definite tomographic abnormalities of the sella turcica.[7] In two reports by Wilson,[6,7] some abnormality on plain skull films was seen in 38 of 40 patients with visual field defects. In our own series of 55 patients (Table 3), 19 had visual field defects. In only one patient (a 17-year-old girl with craniopharyngioma) were abnormalities of the sella turcica absent on plain skull films. Others have also observed a similarly high frequency of abnormalities seen on radiographic studies of patients with visual field impairment.

Radiologic Techniques

Either because of headache evaluation or, frequently, because of findings of x-ray studies of other parts of the skull (such as the sinuses), suspicion of a pituitary tumor is aroused. A variety of radiologic techniques have been devised to investigate the sella turcica and the structures surrounding the pituitary. We will discuss those which provide the most information with the lowest morbidity.

Plain skull films and tomography. Tumor-induced abnormalities observed on conventional plain x-ray films and tomograms of the sella in-

clude enlargement of the sella, pathological double contour (double floor) and erosions of the lamina dura, the cortical bone which lines the sella turcica. Of those mentioned, erosion seems to be the most diagnostic of a pituitary tumor (Figure 1). Borderline variants of the normal sella turcica have not been completely defined. As a result, false-positive interpretation of a sella mass lesion has initiated numerous searches for tumors that did not exist. Controversy exists in radiologic circles over how to judge normal and abnormal findings. It is difficult to be definite about sella enlargement because the normal range is so wide. Erosion seems to be a more significant finding, especially if found in the floor of the sella. In a study by McLachlan[9] of 141 patients with acromegaly, evidence of minimal abnormalities of the sella turcica was found on plain films and tomograms of 25 patients. These findings were compared with a similar number of plain skull films from patients for whom autopsy studies showed no intrasellar or parasellar pathological condition. Abnormalities of shape, double contour and erosion were found frequently in both groups. Swanson and duBoulay[10] looked at radiographic studies of 85 patients who were thought to be free of pituitary disease. In 31 percent of them a double floor was noted and in 16.5 percent thinning of the lamina dura was detected. Although it has been argued[11] that the incidence of these borderline abnormalities would be consistent with the same percentage of undiagnosed tumors found at autopsy, it seems fair to state that caution should be exercised in overinterpretation of plain film and tomographic findings of sella appearances.

Computerized tomography. Computerized tomographic (CT) scanning is a relatively new tool and therefore there has not been a great deal of experience with it. Because lesions smaller than 1 cm cannot be identified with certainty using CT scanning, small tumors can be missed if this technique is used alone. In a recent study from the Cleveland Clinic,[12] involving 20 patients with surgically confirmed juxtasella lesions, it was found that 19 of the 20 cases were diagnosed by CT scanning. The one patient in whom the diagnosis was not made had an aneurysm. Accuracy was only surpassed by pneumoencephalography. In another study,[13] CT scanning detected all 17 pituitary tumors larger than 1.5 cm, three of five between 1.5 and 0.5 cm and no tumors smaller than 0.5 cm. The accuracy of CT scanning compared with other forms suggests that pneumoencephalography is 100 percent accurate, CT scanning 95 percent, angiography 88 percent, radionuclide scintigraphy 31 percent and skull films 35 percent accurate. Our own experience is given in Table 3; CT scanning was diagnostic in only 33 percent of the cases, that is, in three of nine patients. The three patients had obvious abnormalities of the sella; in two they were detected on plain skull films. In the third patient the plain skull films showed no abnormalities but an obvious craniopharyngioma was found on a CT scan.

Pneumoencephalography. Pneumoencephalograms represent the most definitive tool for defining the anatomy of structures in and around the sella turcica. This technique employs air injected into the subarachnoid space via a lumbar puncture. Rise of the air by gravity to the basal cisterns provides contrast around the pituitary stalk if the patient is seated with brow up. The air enters the ventricular system through the foramina

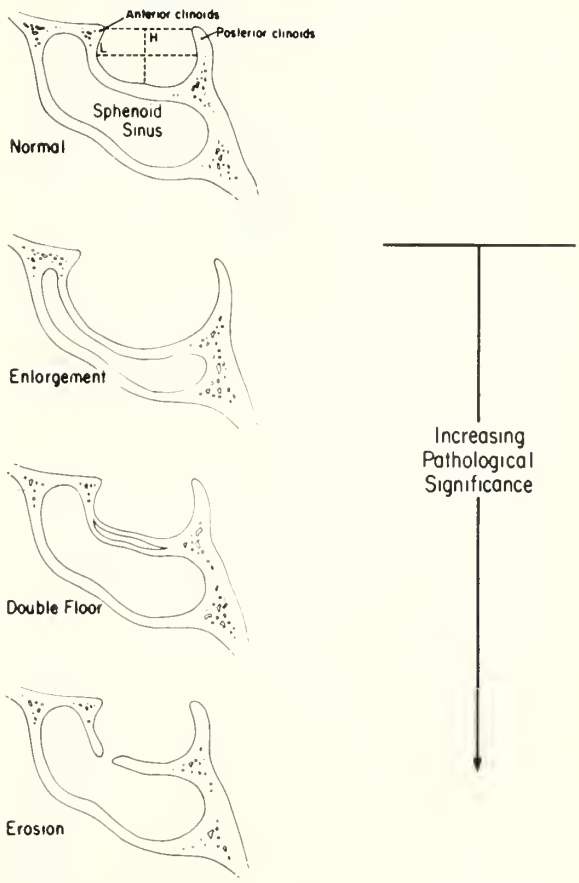

Figure 1.—Schematic diagram showing the most commonly encountered abnormalities of the sella turcica produced by pituitary tumors.

of Magendie and Luschka (Figure 2). An experimental water-soluble contrast agent, metrazimide, recently released in the United States, in the future may replace air as the injected contrast agent. However, mental confusion and convulsions have been reported as complications of this agent. Attempts to use lower concentrations during CT scanning are under study.[14] It is generally accepted that the sella turcica is lined by a dural membrane and occupied by the hypophysis. A reflection of the dura (sella diaphragm) makes a noose around the stalk as it enters the fossa. Air does not usually enter the fossa during a pneumoencephalogram. When it does so, the radiologic diagnosis is referred to as an "empty sella" (Figure 3). Busch[15] noted a complete sella diaphragm in only 42 percent of 788 autopsy cases of patients without pituitary disease. He also noticed an apparently empty sella with compression and flattening of the pituitary against the floor and walls of the sella in 5.5 percent of the cases. In these latter instances, arachnoid membrane herniated into the portion of the sella not occupied by the pituitary.

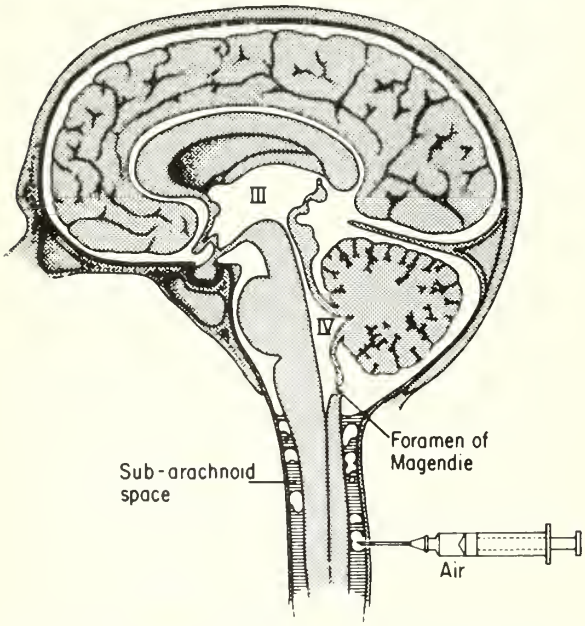

Figure 2.—Artist's interpretation of a pneumoencephalogram. Air is injected via a lumbar puncture into the subarachnoid space and acts as a contrast agent when x-ray films are made.

Randall and colleagues[16] have arbitrarily divided the empty sella syndrome into two categories, primary and secondary. Primary defines idiopathic origin and is presumed to be due to faulty embryologic development of the diaphragm sella, allowing herniation of the arachnoid membrane into the sella, which, in turn, permits compression of normal pituitary tissue by transmitted cerebrospinal fluid pressure. The secondary causes are due to removal of pituitary contents by a surgical procedure or shrinkage from irradiation. Because "empty" sellae have been noted to contain tumors secreting adrenocorticotropic hormone (ACTH), human growth hormone (HGH) or prolactin,[17] spontaneous partial pituitary infarction or unidentified mechanisms may be responsible for an empty sella. Mild bitemporal field defects have been reported in patients with normal pituitary function[18] and an empty sella. It has been found in such cases that optic nerves have herniated into the sella or have remained in their normal position but were thinned.[19]

Because endocrine function has been reported

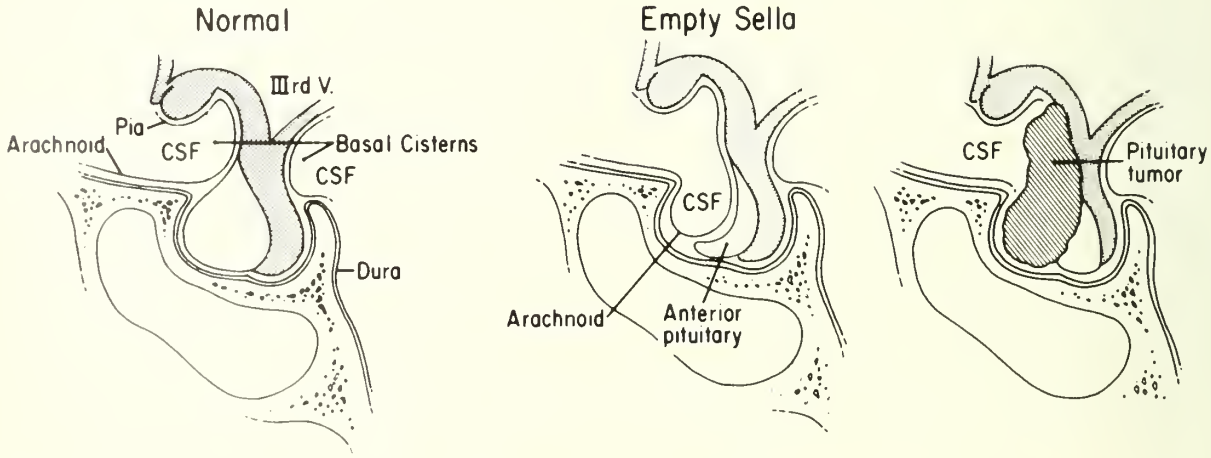

Figure 3.—Schematic diagram showing relationships of the meninges to the normal pituitary (left drawing), herniation of the meninges into an "empty sella" (center drawing) and interruption of the meninges by suprasellar extension of a pituitary tumor (right drawing). (CSF = cerebrospinal fluid)

to be normal,[16] deficient in one or more hormones[20,21] or associated with excess hormone secretion,[17] no hormonal pattern or patterns can specifically identify an empty sella. The empty sella syndrome has been suggested in obese middle-aged women with mild hypertension and a large sella without erosion.[22] Due to the variability in the mechanisms of pituitary tumor presentations, these constellations of findings could also be caused by a pituitary tumor. At present, pneumoencephalography seems to be the most reliable method of diagnosing the syndrome of empty sella.

Hormonal Investigation of Pituitary Tumors

Hormonal Tests to Identify Pituitary Tumors

Pituitary tumors can secrete excessive amounts of one or more hormones or have no alteration in pituitary hormonal function.[3] Excessive amounts of growth hormone can be identified best by observing the response of HGH in plasma to administration of a glucose load. Failure of growth hormone concentrations in serum to be suppressed to within normal range following oral administration of glucose has been considered a criterion for the diagnosis of acromegaly.[23,24] In a series of 50 patients[25] with acromegaly, suppression of HGH to below 15 ng per ml occurred in only two patients; and in these two, it was not suppressed to undetectable levels.[23] Paradoxical responses of serum growth hormone to glucose have been observed in patients with acromegaly,[26] in those with tumors encroaching on the hypothalamus and in those with a variety of disorders without recognized structural lesions of the hypothalamus or pituitary.[27] In patients with acromegaly, secretion of human growth hormone often can be stimulated by thyrotropin-releasing hormone (TRH), which does not normally provoke HGH release.[29] These observations have led authors to suggest a role of the hypothalamus[25] in causing acromegaly. Our experience suggests that acromegaly is not a hypothalamic disease because pituitary adenomectomy seems to cure excess secretion of growth hormone.[30]

Although suppression of growth hormone secretion by glucose seems to be an excellent way of identifying excess growth hormone secretion, tumor secretion of prolactin is not easily determined. Because secretion of prolactin is predominantly under inhibitory control, any process that diminishes hypothalamic control over the pituitary can cause increased release of prolactin. Clinically, it is difficult to differentiate between excess prolactin secretion caused by decreased hypothalamic control and excess caused by a tumor. A variety of stimulatory and inhibition tests have been devised to show tumorous origin. None of these has been completely reliable. Table 4 lists tests used to identify pituitary tumors secreting excess growth hormone, prolactin or ACTH. It can be seen that hormonal suppression tests for ACTH and growth hormone are very infrequently accompanied by false-positive responses. Contrary to this experience, when stimulation or suppression testing has been used to identify prolactin-secreting pituitary tumors, nontumorous pituitary-dependent prolactin responses are common. A single serum prolactin sample, we feel, is as reliable as multiple samples during stimulation or suppression tests for this hormone. When excessive prolactin secretion is observed, verification of pituitary tumor origin should depend on radiologic or ophthalmologic evidence, or both.

If there are no abnormal clinical features of hormonal excess or deficiency, but x-ray studies suggest a pituitary tumor, laboratory evidence of excess or deficient anterior pituitary hormones should be established. It is difficult to say with certainty which tests should be done. Because asymptomatic hyperprolactinemia may accompany two thirds of all pituitary tumors,[43,44] a

TABLE 4.—*Blood Tests Commonly Used to Identify Pituitary Tumors Secreting Excess Human Growth Hormone, Prolactin or ACTH*

Hormone and Ref. No.	*Test*	*Normal Response*	*Tumor Response*	*False-Positive Responses*
HGH[23,24,31]	Orally given glucose	Decrease to <5 ng/ml	No change	Infrequent
Prolactin[32-35]	Isolated sample	<20 ng/ml	>100 ng/ml	Frequent
Prolactin[31-33]	Orally given phenothiazine	Double baseline	No change	Frequent
Prolactin[32,33,36-38]	Intravenously given TRH	Double baseline	No change	Frequent
Prolactin[32,33,36,37,39,40]	500 mg levodopa orally	Decrease to <50% baseline	No change	Frequent
ACTH[41,42]	Orally give dexamethasone	Urinary 17-hydroxycorticosteroid suppression	Resistance to suppression	Infrequent

ACTH = adrenocorticotropic hormone; HGH = human growth hormone; TRH = thyrotropin-releasing hormone

serum prolactin determination is a mandatory part of the laboratory evaluation. Excess growth hormone should be documented by determining its serum level during a glucose tolerance test. Because unrecognized primary hypothyroidism may cause enlargement and erosion of the sella turcica,[45,46] serum thyroxin and thyroid-stimulating hormone (TSH) tests are also warranted. Normal sexual function and menstrual periods would obviate the need for determining levels of serum estradiol and luteinizing hormone (LH) in female patients, but any menstrual irregularity would warrant these tests. Serum testosterone and serum LH values in males should also be obtained because hypogonadism in males may accompany hyperprolactinemia or a pituitary tumor that is destroying normal pituitary tissues. ACTH reserve should be tested by metyrapone or insulin tolerance to confirm the need for exogenous cortisol if an operation is contemplated.

Estimation of Hormones in Cerebrospinal Fluid

Estimation of hormones in cerebrospinal fluid has been introduced by Linfoot and co-workers[47] and experience has been greatly expanded by Jordan and Kendall.[48] Anterior pituitary hormones such as growth hormone, TSH, LH and follicle-stimulating hormone (FSH) are normally undetectable in cerebrospinal fluid (CSF) or found in very low concentrations as is the case with ACTH and prolactin. Normal secretion of pituitary hormones occurs by a process of exocytosis of hormone granules into blood. The pituitary is not normally surrounded by cerebrospinal fluid but is covered by meninges. These two factors explain why pituitary hormone concentrations in cerebrospinal fluid are normally low. It is presumed that pituitary tumors by local extension break through meninges and are in direct contact with cerebrospinal fluid. In addition, hormone secretion from tumors is not entirely into the blood but hormones also are secreted locally by a process called misplaced exocytosis. Kendall and Jordan[48] found that in 21 of 22 patients with suprasellar extension, levels of one or more hormones were elevated in cerebrospinal fluid. Unfortunately, not all tumors with suprasellar extension have elevated hormone levels in CSF. Also, because many tumors do not have suprasellar extension they cannot be identified by examining hormone levels in CSF. Further experience is needed with this tool before its exact role in pituitary tumor diagnosis can be appreciated.

Therapy for Pituitary Tumors

Surgical treatment of macroadenomas (tumors extending above or outside the pituitary fossa) is necessary because irradiation of pituitary tumor tissue above the sella can cause damage to hypothalamic tissue.[8] Therapy for microadenomas is controversial. Some investigators have maintained that endocrine-active tumors are not responsive to irradiation.[49] If successful, irradiation may take years to reduce hormonal levels to normal, or to reach maximum effect.[50,51] The time required for hormone levels to return to normal varies with the type of disease and the method of radiation therapy, such as conventional, supervoltage, x-ray, alpha-particle, proton beam or photon.[50-52] Surgical techniques, especially the transsphenoid approach, must await long-term follow-up because the hypothalamus may play a role in tumor pathogenesis and cause new tumor development in the remaining normal pituitary tissue. Therapeutic choices may become clear when a prospective randomized trial has compared the effects of irradiation with results of surgical approaches to pituitary tumor therapy. We have selected a transsphenoidal operation whenever possible because it achieves both reduction of excess hormones and decompression rapidly. We prefer to think that most tumors are not caused by excess hypothalamic stimulation.[30] The success or failure of surgical therapy cannot yet be predicted; however, it has been noted that patients with large invasive tumors do poorly whereas those with smaller, intrasellar and noninvasive tumors fare much better.[53]

One drug that has shown promise in controlling excess secretion of growth hormone or prolactin is bromocriptine, an ergot alkaloid (2-bromoergocryptine CB-154) which has properties of a long-lasting dopamine agonist. It raises serum growth hormone levels in normal subjects but paradoxically lowers them in patients with acromegaly.[54,55] Relapse occurs after administration of this drug is stopped and therefore, its use cannot be considered definitive therapy. In cases of unsuccessful surgical treatment or irradiation (or both) of tumors secreting excess prolactin[32,56] or growth hormone, this drug would seem to have a definite role.

In cases of these tumors our present approach (Figure 4) is to suggest surgical treatment whenever possible, especially when preservation of remaining normal pituitary tissue is important,

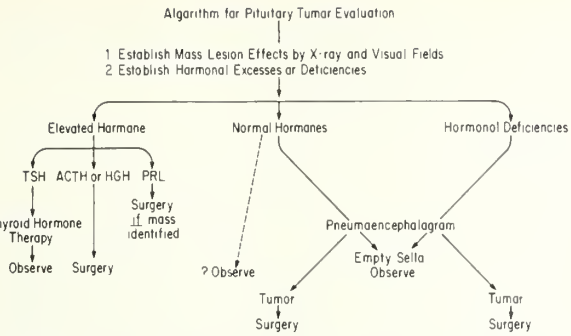

Figure 4.—Author's algorithm, suggesting therapeutic courses for different clinical situations encountered during the evaluation of patients with suspected pituitary tumors. (ACTH = adrenocorticotropic hormone; HGH = human growth hormone; PRL = prolactin; TSH = thyroid-stimulating hormone.)

such as in young persons interested in fertility. When an operation is refused or considered unsafe due to advanced age or debility, other forms of therapy should be considered. The choice of therapy depends on a variety of factors, such as which hormone is produced in excess, the extent of suprasellar growth and previous therapy. ACTH-producing pituitary tumors have been successfully treated by pituitary adenomectomy.[57,58] When surgical treatment for excess ACTH is not feasible, we suggest radiation therapy with protons or alpha particles,[59] which in adults is more successful than conventional irradiation.[60] However, cobalt 60, a source of protons, has been effective in patients with childhood Cushing disease.[61] We consider drug therapy for Cushing disease temporary because relapse occurs after discontinuation. No drug for this disorder reduces tumor size. Attempts to treat Cushing disease as a hypothalamic disorder, using cyproheptadine,[62] a serotonin antagonist, or naloxone,[63] a narcotic antagonist, have had limited success and must be considered experimental.

When a surgical procedure is not possible for patients with HGH-secreting tumors, we suggest irradiation. For HGH-producing tumors there does not seem to be clear-cut superiority of particle irradiation over conventional radiation therapy.[50] In the past a variety of drugs have been tried to control excess HGH secretion without success until bromocriptine became available. Not all cases respond,[54] however, and at present there is no means of predicting which will. We treat patients with prolactin-secreting tumors by conventional irradiation when an operation is not feasible. Surgical treatment is not suggested for excess prolactin secretion unassociated with radiologic evidence of a pituitary tumor because causes of hyperprolactinemia other than a pituitary tumor are not uncommon. It should be noted that galactorrhea and amenorrhea have been associated with pituitary tumors and normal levels of serum prolactin, suggesting intermittent hypersecretion.[64] Drug therapy for prolactin-secreting tumors with bromocriptine has been a significant advancement. There are some studies[65,66] that suggest this drug may reduce the size of prolactinomas. Further experience with this form of medical therapy will delineate which patients are best treated primarily with this drug.

In the algorithm given in Figure 4 we do not suggest pituitary surgical procedures for excess TSH secretion and concomitant hypothyroidism because enlargement of the pituitary can be observed in primary hypothyroidism.[45] If there is an increased level of TSH in a patient with hyperthyroidism and pituitary enlargement,[67] then an operation would be suggested.

There is no easy answer concerning treatment of a patient with a borderline abnormality of the sella turcica and normal pituitary hormone function. Should such a patient be subjected to pneumoencephalography, or should the condition just be observed? With elderly patients the case should most probably be observed. It is more difficult to give specific guidelines for treating young patients. In the future, criteria for normal borderline variants of the sella may help us with this decision.

We are embarking on a prospective study to ascertain which patients with pituitary tumors are best treated by transsphenoidal adenomectomy. Perhaps after our study and similar others, the exact role of surgical procedures will surface.

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Treatment of Acromegaly, Cushing Disease and Nelson Syndrome

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Since 1957 we have treated more than 429 patients who had pituitary neoplasms, most of which were hormone-secreting tumors. Long-term follow-up in the large group of patients treated for acromegaly shows a median survival of better than 16 years, with improvement over time. The short-term follow-up results in patients with Cushing disease, Nelson syndrome and chromophobe adenoma are very encouraging. To compare these excellent results with those following surgical procedures, a large study of patients followed for a long period after the operations is needed.*

SINCE 1957 we have had an intensive experience in the study, diagnosis and treatment of acromegaly, Cushing* disease and Nelson syndrome. This report emphasizes the long-term results chiefly in treating patients with acromegaly. Previous reports have given extensive information regarding the methods used, the physical aspects and dosimetry of the radiation and the many detailed metabolic studies.[1-12] In the past and present as well, these disorders have been and are treated by surgical procedures or by conventional pituitary irradiation, or both. However, in our work, heavy-particle irradiation (plateau or Bragg Peak) has been used,[13] administered with the aid of a stereotactic setup to hold the patient's head firmly, and by head and body rotation, to limit to safe levels the amount of radiation delivered to the cranial nerves and temporal lobes.

During the "Cushing era" patients with Cushing disease were treated with standard roentgen irradiation[14-17] The treatment was first carried out by Dr. Merrill Sosman, a radiologist at the Peter Bent Brigham Hospital in Boston. However, the doses given were insufficient.[17] The first patient receiving this treatment at Peter Bent Brigham Hospital was diagnosed as having a large basophilic adenoma. Several years later the patient died and a postmortem examination showed a large basophilic adenoma of the pituitary. In the intervening years many patients with Cushing disease have been treated by bilateral adrenalectomy. However, in recent years it has become recognized that the primary defect is either in the pituitary gland itself or in the hypothalamopituitary adenal axis, and the point of attack should be the pituitary gland. More recently, with the "rediscovery" of transsphenoidal pituitary operations, a greater number of patients with Cushing disease are being treated by hypophysectomy, with removal of either microadenomas or macroadenomas.[18] However, there has not been adequate follow-up time, especially for those with acromegaly, in any large series of such patients to allow analysis of long-term effects regarding the return to normal of metabolic findings and the relief of clinical symp-

*THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. A explanation may be found on page 78 of the July 1978 issue.

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toms and signs. It will be another five or more years before such a series of patients will have been followed long enough for comparison with our series.

Patients and Methods

We have treated 429 patients with alpha-particle pituitary irradiation (APPI, also referred to as heavy-particle pituitary irradiation [HPPI]) since 1957. These patients had pituitary tumors, most of which caused hormonal hypersecretion. As stated above, in treating these patients we used a beam of alpha particles or protons, employing a stereotactic method for alignment of the pituitary sella and delivering to the pituitary gland doses close to twice that delivered by the usual photon method (Figure 1). In this way, we have observed some remarkable results. The method consists of rotation of the patient's head right and left through angles of 30 degrees and by simultaneous rotation of the body. Thus, one is able to deliver to the pituitary gland a much larger dose than is possible with photons, without damage to the nervous tissue such as the cranial nerves and the temporal lobes.

In computerized settings of the dosage schedule for each patient, it is calculated that less than 3,000 rads be directed to the temporal lobe and, on the average, 6,000 rads are given over five days. In some patients, especially in the early cases, we used the so-called Bragg peak,[19] as has Kjellberg,[20] who also has had extensive experience with Bragg peak protons. We also treated a few patients who had received previous photon irradiation, but since 1961 this has been discontinued and we no longer treat any patients who have had previous radiation therapy. We no longer use the Bragg peak because of the difficulty of exact alignment. Recent work, however, with another new beam of much heavier particles such as carbon 12 or neon, and a method of so-called autoradioactive localization for the location of the peak, should make it possible to give larger doses than are given now by the direct beam plus head and body rotation.[4] This will be especially important in the case of Cushing disease where, at present, some patients should be given medical treatment with metyrapone or aminoglutethamide, or both, for several months until the effects of radiation have taken place. Some of these patients

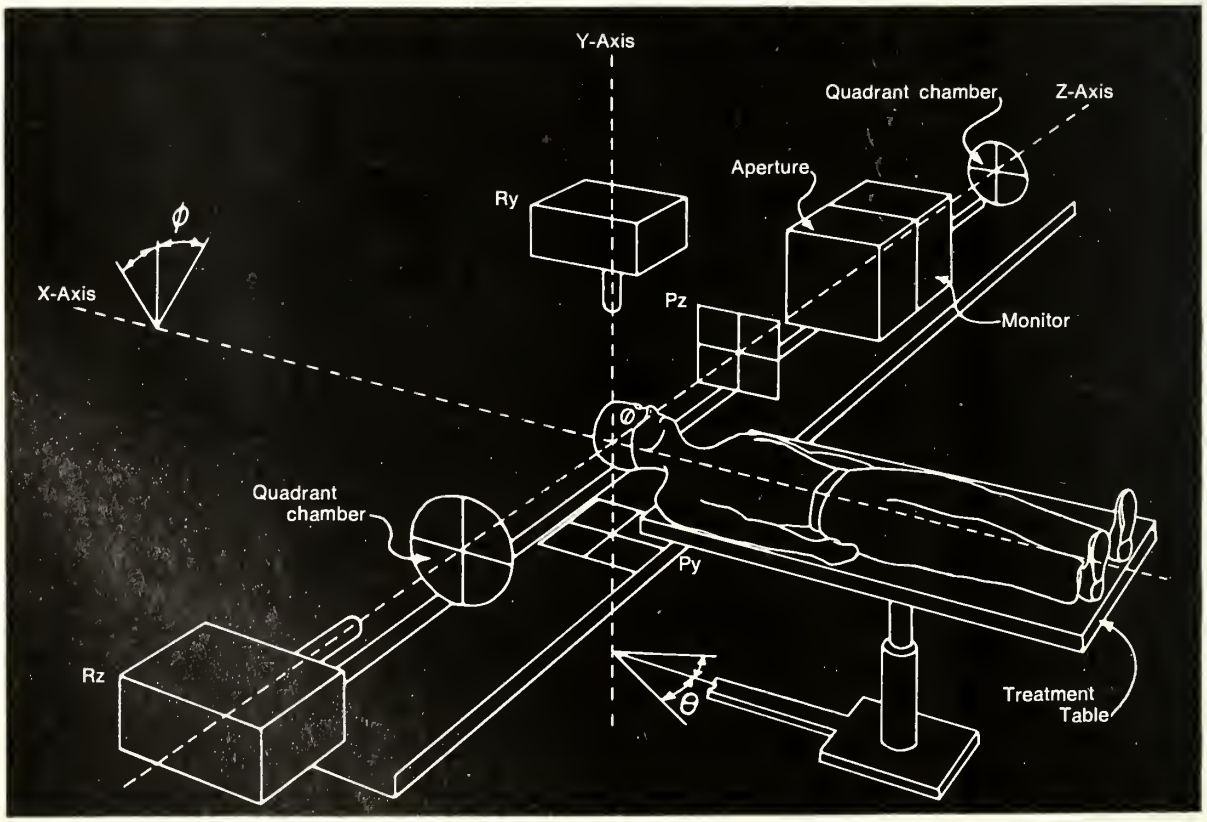

Figure 1.—Diagram of the stereotactic setup for administration of heavy-particle irradiation to the sella turcica. Reproduced by permission from Am J Roentgenol Radium Ther Nucl Med 67:2, 1952.

require higher doses of radiation than we can now give. We have found by using all available methods for visualization of the sella turcica that the most reliable are pneumoencephalography and computerized tomographic (CT) scans. In all patients who are treated by the ion beam methods such studies are carried out to avoid treating patients with suprasellar extensions or massive sphenoid extension. However, we do treat patients who have sphenoid extensions in cases where we can appropriately place the beam. Although visual field defects are usually associated with suprasellar extension, we have treated a few patients who had very small defects. The goals of the treatment are to relieve or minimize symptoms and signs and to try to return metabolic findings to normal (Figure 2).

Figure 2.—Patient before treatment for acromegaly and ten years later. After treatment soft tissue regression has taken place and human growth hormone levels became normal. Reproduced by permission from J Clin Endo Crinol Metab 31:188, 1970.

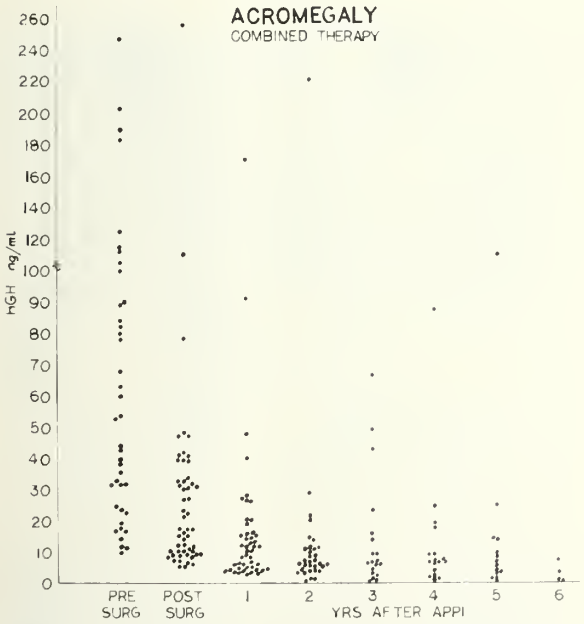

Figure 3.—Human growth hormone (hGH) values for patients before and after unsuccessful surgical treatment, and after alpha-particle pituitary irradiation (APPI, also referred to as heavy-particle pituitary irradiation [HPPI]). Reproduced with permission from Linfoot JA (Ed): Recent Advances in the Diagnosis and Treatment of Pituitary Tumors, Raven Press, New York, 1979.

Acromegaly

Many of the patients with acromegaly had had previous unsuccessful operations, usually transsphenoidal surgical excisions. Figure 3 shows human growth hormone (HGH) values in a group of patients before and after these unsuccessful operations, and after heavy-particle pituitary irradiation (HPPI). Figure 4 shows growth hormone levels in all of our patients with acromegaly before and after HPPI. Figure 5 compares survival of patients with acromegaly after therapy (median 16 years) with survival in a diabetic population and expected survival in an age-matched population. It should be mentioned that as a group our patients have often been refused surgical treatment for various reasons. In general, our patients are selected if the beam can be placed accurately. If not, we refer such patients for surgical treat-

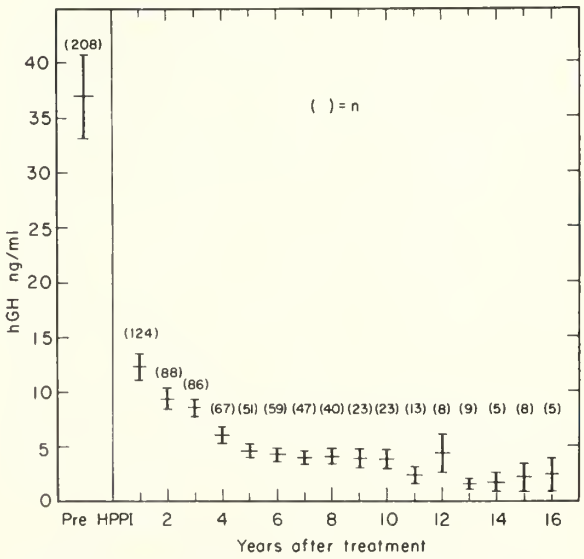

Figure 4.—Human growth hormone (hGH) values in patients with acromegaly before and after heavy-particle pituitary irradiation (HPPI). Reproduced with permission from Linfoot JA (Ed): Recent Advances in the Diagnosis and Treatment of Pituitary Tumors, Raven Press, New York, 1979.

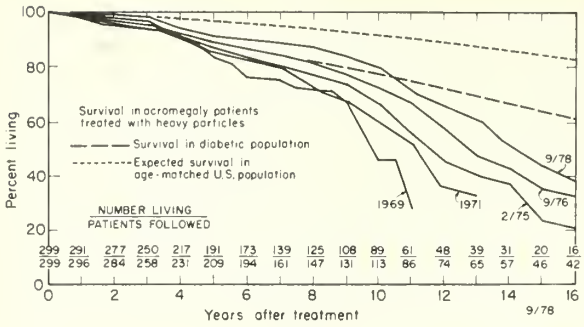

Figure 5.—Survival of patients with acromegaly after heavy-particle pituitary irradiation compared with survival in a diabetic population and expected survival in an age-matched population. Reproduced with permission from Linfoot JA (Ed): Recent Advances in the Diagnosis and Treatment of Pituitary Tumors, Raven Press, New York, 1979.

ment. In the early part of our work, before 1961, we had patients with rare neurological complications; however, since then less than 1 percent of the patients have had any such complications. Table 1 indicates the age and sex distribution of patients with acromegaly and the delay before patients are referred for treatment.

Cushing Disease

There are 64 patients in this group; of these, 59 had normal sellar sizes. The diagnosis was made by the usual clinical and metabolic findings, including the dexamethasone suppression test and a metyrapone test. After therapy, replacement therapy with cortisone was necessary in 9 percent of these patients, thyroid replacement in 16 percent and gonadal replacement therapy in 11 percent. There were two deaths: one patient died of cerebrovascular complications unrelated to the Cushing disease, which was under control. The other was a patient in a mental hospital in whom Cushing disease was also under control. There were no other complications. This series is being increased in number, and longer years of follow-up will be necessary for comparison with long-term results in patients treated surgically.[18]

Figure 6 shows a patient with Cushing syndrome before and after therapy. After treatment cortisol levels and most of the symptoms returned to normal.

Nelson Syndrome

By Nelson syndrome we mean what Nelson has termed the third stage of Cushing syndrome,[21] and which he describes as having the following characteristics:

A third stage (most common after total adrenalectomy) in which plasma ACTH levels are often at extremely high levels, the patients are intensely pigmented and the plasma ACTH is poorly suppressed by the administration of exogenous cortical steroid. This group of patients is most often found to have pituitary tumors, although such tumors have been described in the earlier stages of the disease.

According to reports of several authors,[21-28] pituitary tumors have developed in about 10 percent of patients with Cushing disease associated with adrenocortical hyperplasia who had been treated initially with total adrenalectomy. These authors expressed concern that adrenalectomy may serve as a triggering mechanism (lack of feedback) that is responsible for the clinical ap-

TABLE 1.—*Age and Sex Distribution of 294 Patients With Acromegaly Treated With Heavy-Particle Pituitary Irradiation*

Patients		Age (years)		Duration (years)
Sex	*Number*	*At Time of Heavy-Particle Therapy Median (Range)*	*At Time of Onset of Signs and Symptoms Median (Range)*	*At Time of Heavy-Particle Therapy Median (Range)*
Male	181	39.8 (15-69)	31.2 (13-59)	7.2 (1-40)
Female	113	48.0 (15-68)	36.8 (13-63)	8.4 (1-29)
TOTAL	294	43.5 (15-69)	34.5 (13-63)	7.7 (1-40)

Figure 6.—Patient with Cushing disease before and after therapy. After treatment there is a loss of the Cushinoid features, such as striae and obesity. Reproduced by permission from Transactions of the American Clinical and Climatological Association, Vol. 81, 1970.

pearance and rapid growth of the pituitary tumors. Orth and Liddle[25] reported that in 19 patients treated first by pituitary irradiation and later by bilateral adrenalectomy, no evidence of pituitary tumors was found during a follow-up period of 1 to 13 years. They pointed out the possibility that in patients who had received pituitary irradiation before total adrenalectomy large pituitary tumors are less likely to develop. However, Wild, Nicolis and Gabrilove[28] cited two of their patients who initially had undergone unilateral adrenalectomy and pituitary irradiation (conventional radiotherapy). These patients subsequently required total adrenalectomy to control their disease and, later, skin pigmentation and pituitary tumors developed. The authors concluded that experience to date indicates that pituitary irradiation may reduce the incidence of Nelson syndrome, but that its effectiveness had not been precisely established. We also have observed Nelson syndrome in two instances after treatment of patients with Cushing disease.

There have been 15 patients in the study with Nelson syndrome. Six had unsuccessful surgical treatment before receiving HPPI. There has been one death due to an invasive tumor, which is not uncommon in patients with tumors that secrete adrenocorticotropic hormone (ACTH). There were no other complications, and the pigmentation of the skin either disappeared or decreased in all patients treated.

Prolactin Tumors

We have had limited experience in treating patients with prolactin-secreting tumors. Of the 29 treated, nine had previous unsuccessful hypophysectomies. Five patients had sellar volumes of less than 1,100 cu mm in size and thus were considered to have microadenomas. The other patients had grade II, III or IV lesions, with relatively large sella turcicas. About 10 percent of these patients required adrenal cortisone replacement therapy. However, in general, the patients have had a lowering of prolactin levels and disap-

TABLE 2.—*Patients With Pituitary Tumors Treated With Heavy-Particle Pituitary Irradiation*

	Number of Patients			Survival, Years After Heavy-Particle Therapy											
				1		1-2		3-4		5-9		10-14		15-19	
	Total	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead
Acromegaly	294	268	26	10	5	53	3	37	10	110	3	44	3	14	2
Cushing disease	54	52	2	5	1	19	0	3	0	15	1	9	0	1	0
Nelson syndrome	14	13	1	1	0	3	0	2	1	4	0	2	0	1	0
Chromophobe adenoma	32	27	5	2	0	4	2	4	2	10	1	5	0	2	0
Prolactin-secreting adenoma	16	16	0	4	0	5	0	4	0	2	0	1	0	0	0
TOTAL	410	376	34	22	6	84	5	50	13	141	5	61	3	18	2

TABLE 3.—*Cyclotrons and Synchrotrons Capable of Producing Heavy Particles With Sufficient Energy for Therapeutic Use*

Location of Cyclotron or Synchrotron	*Proton Energy*
University of Maryland, College Park, Maryland	100 MeV
Harvard University, Cambridge, Massachusetts	160 MeV
University of Rochester, Rochester, New York	240 MeV
Columbia University, Irvington, New York	385 MeV
Carnegie Institute of Technology, Pittsburgh, Pennsylvania	440 MeV
University of Chicago, Chicago, Illinois	450 MeV
NASA-Langley Research Center, Langley Field, Virginia	600 MeV
Lawrence Berkeley Laboratory (184″), Berkeley, California	730 MeV
Princeton University, Princeton, New Jersey	3 BeV
Lawrence Berkeley Laboratory (Bevatron), Berkeley, California	9 BeV
McGill University, Montreal, Quebec, Canada	100 MeV
College de France, Orsay, France	155 MeV
Atomic Energy Research Establishment, Harwell, England	175 MeV
University of Uppsala, Uppsala, Sweden	185 MeV
Institute for Theoretical and Experimental Physics (ITEP), Moscow, U.S.S.R.	200 MeV
University of Liverpool, Liverpool, England	381 MeV
European Council for Nuclear Research (CERN), Geneva, Switzerland	600 MeV
Joint Institute for Nuclear Research (JINR), Dubna, U.S.S.R.	680 MeV

pearance of galactorrhea and amenorrhea; and in at least two patients pregnancy has occurred. At present, our experience is not extensive enough for a detailed discussion of the long-term effects of this therapy in these patients.

Conclusions

The most important message of this paper is that to compare the various methods of therapy for pituitary tumors, it is essential that hundreds of patients be followed for many years after treatment. It will require a good many years before the long-term results of surgical treatment of acromegaly can be compared with our results. We emphasize that in the case of acromegaly, the median survival of patients is better than 16 years, and this will improve over time (Figure 5).

It also should be emphasized that patients are not refused our treatment program although many of them had been previously turned away as poor surgical risks elsewhere. As a group, our cases are more complicated than those patients receiving surgical treatment. Table 1 shows that patients with acromegaly are treated approximately eight years after the diagnosis has been made. If the diagnosis is made sooner and treatment administered earlier, it seems that survival may well approach normal.

Death in patients with acromegaly is primarily due to vascular disease. Also, approximately a third of patients with acromegaly have hypertension and about half of these have a return of blood pressure to normal or in the direction of normal after irradiation therapy. The mechanisms of hypertension in these patients are under intensive study in our laboratory, but they are not understood yet. In patients with advanced acromegaly and cardiomegaly (of which we have six) the heart does not return to normal size.

Finally, Table 2 provides a summary of 410 of the patients treated between 1957 and September 1978, and Table 3 lists cyclotrons and synchrotrons which are being used or could be used for heavy-particle pituitary irradiation as described in this paper.

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Tick-borne Relapsing Fever in the Pacific Northwest: An Underdiagnosed Illness?

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Some 30 cases of tick-borne relapsing fever due to Borrelia *are known to have occurred between 1965 and 1978 in the Pacific Northwest. This disease was found more frequently in young men with a history of wilderness exposure during the summer months. Recurrent fever was the most common symptom with temperatures reaching higher than 39.5°C (103.1°F) in all cases, and many patients had three or more febrile episodes. Splenomegaly was the second most common finding reported. Diagnosis of relapsing fever was made in 20 cases by identifying spirochetes on peripheral blood smears. In ten remaining cases the diagnosis was made on clinical and epidemiologic grounds.*

Information regarding therapy was available in 21 cases. Ten patients received a tetracycline drug and all had a prompt response without relapse. Two of the patients died, a 68-year-old woman with possible myocardial involvement and a newborn infant with infection acquired in utero and meningeal involvement.

The diagnosis was often delayed in spite of outpatient evaluation and admittance to hospital, probably because borreliosis was not considered in the differential diagnosis. Because tick-borne relapsing fever is eventually a self-limited disease in most patients, it is probably not recognized often enough. Awareness of this disease and examination of the peripheral blood smear for spirochetes will lead to earlier diagnosis. Prompt initiation of tetracycline therapy should reduce morbidity associated with borreliosis.

RELAPSING FEVER due to *Borrelia* is one of several acute febrile illnesses commonly included in textbook differential diagnoses, but rarely considered in clinical situations. For this reason, many cases are probably missed each year, particularly in the western United States.

Investigation of a recent case of this disease led to the detection of several more related cases. Further research uncovered 26 unpublished cases plus three previously described cases, supporting the authors' suspicion that relapsing fever is not recognized with sufficient frequency.[1,2]

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This paper presents an index case, a report of an additional case and features of another 28 cases, as well as a review of the literature. Because the diagnosis of relapsing fever can be made by simple examination of the peripheral blood smear, greater familiarity with its characteristics and an appropriate index of suspicion of its presence should result in earlier and more frequent diagnosis.

Patients and Methods

This report is based on data obtained from the Public Health Departments in Oregon and Washington and a hospital located in the area where the index patient became infected. Clinical data available in health department records were meager in several cases. Therefore, no quantitative estimate of the frequencies of signs and symptoms could be made.

Cases described in this report are classified as definite, if spirochetes were found on smears of peripheral blood (20 of 30 cases); or probable, if patients had an unexplained recurrent febrile illness that coincided in time and place with a case of relapsing fever confirmed by findings on blood smears (10 of 30 cases). These cases were seen from 1965 to 1978 and do not include an outbreak of 11 cases in eastern Washington reported recently.[3] Included in this series, however, are three previously published cases of patients: a newborn infant with in utero acquisition of meningeal infection, the infant's mother[1] and a 25-year-old college student.[2]

Analysis of 30 Cases

Epidemiology

The disease typically occurred in patients younger than 40 years old (83 percent), with a mean age of 24.6 years. Of the patients, 63 percent were male. All cases occurred in persons who had been in wooded, high, arid regions of Oregon, Washington or Idaho; two thirds occurred in Deschutes County which lies on the eastern face of the Cascade Mountains in Oregon. Most cases of the disease developed during the months of May to September (Figure 1) and 60 percent occurred between 1976 and 1978.

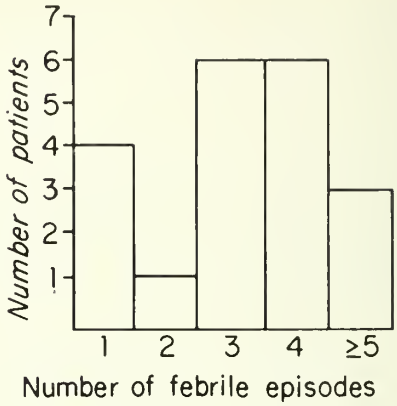

Figure 2.—Number of febrile episodes experienced per patient.

Clinical Presentation

Although the clinical data available for each patient varied considerably, a composite of recorded symptoms accurately reflects a characteristic clinical presentation. Recurrent fever, the most common symptom, occurred in all but four patients in whom a diagnosis was made and treatment begun during the first fever cycle (Figure 2). The temperature was higher than 39.5°C (103.1°F) in all cases. The onset of fever was acute and dramatic as was its resolution. Of the 20 patients in whom descriptions of fever patterns

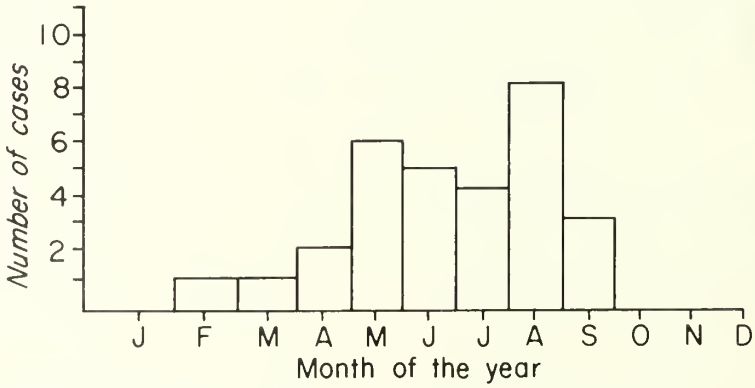

Figure 1.—Occurrence of 30 cases of relapsing fever by month of the year.

were available, 15 had three or more febrile episodes. The four persons whose conditions were diagnosed and treated during the first episode of fever included the index patient described below, an infant born to an infected mother, a 25-year-old man admitted to Duke University Medical Center whose peripheral blood smear was being evaluated for malarial parasites when spirochetes were noted, and a 27-year-old man from Deschutes County whose blood showed the heaviest spirochetemia seen in that region (one or more spirochetes per oil-immersion field). At least three patients with fever were admitted to hospitals and discharged without a diagnosis before borreliosis was recognized during a subsequent febrile period. Many had seen physicians as outpatients one or more times before a correct diagnosis was made. Ten cases were diagnosed retrospectively on clinical and epidemiologic grounds.

Other symptoms mentioned frequently were chills, sweating, malaise, anorexia, myalgia, cough and headache. After fever, splenomegaly was the most commonly recorded physical sign.

Diagnosis

The diagnosis was confirmed by detection of spirochetes in peripheral blood smears in 20 cases (Figure 2). Nine cases (30 percent) of relapsing fever showed no connection with any associated cases. However, it was shown that 7 definite cases were directly associated with 14 coincident cases. The 14 cases had been recognized because of their connections with the 7 "primary" cases, and at least 7 of these 14 patients had already consulted a physician before the correct diagnosis was made.

Response to Therapy

Information regarding therapy was available in 21 cases. Ten patients treated with tetracycline or a tetracycline derivative had prompt response to therapy. Five patients were given penicillin. One of the latter patients had a relapse, but subsequently responded to tetracycline. Both of the patients who died had been treated with penicillin and a second drug—the 68-year-old woman (case 2) had been given penicillin and kanamycin and a newborn infant had received penicillin and chloramphenicol. Four patients had Jarisch-Herxheimer reactions. At least seven patients received no therapy but had a gradual resolution of symptoms.

Reports of Cases

CASE 1. A 30-year-old man employed by the US Forest Service came to the University of Washington Hospital emergency department following two days of spiking temperatures to 40°C (104.0°F), shaking chills and progressive weakness, malaise and myalgias. He had been staying in a cabin in Bull Prairie, Oregon, where another person (a patient included in this report)had become ill three weeks earlier. The other patient had been admitted to hospital in a nearby town. We called the hospital and were told that the patient in question had been diagnosed as having relapsing fever. Our patient was unaware of any recent tick bites.

On physical examination, the patient's temperature was 39.6°C (103.3°F) and an erythematous, papular rash and several ecchymoses were noted. Bruising was easily induced and a Rumpel-Leede test was positive. The neck was supple. An examination of the heart and lungs showed no abnormalities. The abdomen was obese with hypoactive bowel tones and a hepatic span of 10 cm. Results of a neurological examination were within normal limits.

Analysis of urine showed proteinuria (2+) and two to eight erythrocytes per high-powered field; otherwise, findings were normal. The hematocrit, leukocyte count and differential were within normal limits. Platelet count was 98,000 per cu mm. The total bilirubin was 3.2 mg per dl, alkaline phosphatase 65 units per liter (normal 20 to 105 units per liter) and serum aspartate aminotransferase transaminase (formerly serum glutamic oxaloacetic transaminase, SGOT) 144 units per liter (normal <25 units per liter). A Wright-stained smear of peripheral blood was positive for spirochetes (Figure 3).

A study of coagulation times gave these results: the prothrombin time was 15 seconds with a control of 12.5 seconds and 54 percent activity. Partial thromboplastin time was 57 seconds with a control of 39 seconds; a 1:1 mix with normal serum corrected the patient's time to 45 seconds. Thrombin time was 27 seconds with a control of 19. Fibrinogen was 326 mg per dl and fibrin degradation products were more than 10 but less than 40 μg per ml.

The patient was treated with 500 mg of tetracycline given orally every six hours. Defervescence occurred within 24 hours with rapid resolution of the other symptoms. Serial measurements of co-

agulation times showed progressive improvement and values obtained 36 hours after admission had returned to normal. Thrombocytopenia persisted, however, and the platelet count at the time of discharge on the third hospital day was 78,000 per cu mm.

CASE 2. A 68-year-old woman was admitted to an Oregon community hospital on August 19, 1968, with complaints of fever, chills, shortness of breath and chest pain. Several days earlier the patient had been fishing on a nearby river and claimed to have been "bitten by chiggers." Subsequently, there was an abrupt onset of dyspnea, orthopnea, nonproductive cough and pleuritic chest pain of the left anterior quadrant. She had no known history of any cardiopulmonary disorder. The patient was first seen by a local physician and then admitted to hospital with a preliminary diagnosis of congestive heart failure secondary to acute viral myocarditis.

On initial examination, the temperature was 39.0°C (102.2°F), heart rate 108 beats per minute and blood pressure 94/50 mm of mercury. She appeared acutely ill. No rash was noted. Rales were present posteriorly over the lower third of both lung fields. Findings of cardiac examination appeared to be normal. The liver extended 3 cm below the left costal margin and was tender. Trace pedal edema was present.

The hemoglobin value was 12.3 grams per dl and the leukocyte count was 17,000 per cu mm with 85 percent neutrophils, 8 percent lymphocytes and 7 percent monocytes. The erythrocyte sedimentation rate was 114 mm per hour. Serum lactic dehydrogenase was 420 units per liter (normal <290), creatine phosphokinase 3 units per liter (normal 5 to 100) and SGOT 53 units per liter. An electrocardiogram showed low frontal plane voltage with diffuse ST and T changes, as well as an intraventricular conduction delay consistent with incomplete left bundle branch block.

The patient was placed on a cardiac monitor and a transient supraventricular tachycardia was noted and treated with lidocaine. She received no antibiotics for the first 24 hours and her temperature pursued a hectic pattern with late afternoon elevations on two days reaching 40.5°C (104.9°F). On the second hospital day, therapy with administration of penicillin and kanamycin was begun. Twelve hours later, corticosteroid therapy was started when the patient showed deteriorating mental status and worsening dyspnea. The following evening, the patient's condition was noted to have improved, with a clear sensorium and less shortness of breath. She continued to do well until the fourth hospital day when severe cardiac dysrhythmia occurred, and she died suddenly. The presence of spirochetes in six blood culture samples was later confirmed by the Oregon Public Health Department laboratory.

Discussion

Borreliosis was known as a clinical entity by Hippocrates but it did not receive the name of relapsing fever until 1843. The agent was first discovered by Obermeier in Berlin in 1861, and Motschutkoffsky first fulfilled Koch's postulates in 1876 by injecting subjects (including himself) with serum from an infected patient. Münch first showed that the disease could be transmitted by an arthropod vector, and the tick-borne hypothesis as a major mechanism of disease transmission was advanced by Nicole and Anderson in 1927.[4]

There are two types of relapsing fever, tick-borne (endemic) and louse-borne (epidemic). There have been an estimated 50 million cases worldwide of relapsing fever in the first half of this century, with an average mortality of 10 percent.[4] The vast majority of these cases have been louse-borne and have occurred outside the United States.

The first account of the disease in the United States was reported in Philadelphia in 1844. Relapsing fever in this country is almost exclusively tick-borne; and the earliest outbreaks of relapsing fever, occurring in Philadelphia and New York, are the only known louse-borne cases. The first endemic focus of tick-borne relapsing fever was recognized in Colorado in 1915, and this variety has continued to occur sporadically ever since. Some 322 cases were reported in California between 1921 and 1961. The first case reports from Washington were by Davis in 1932,[5] and Hemingway reported the first case from Oregon in 1940.[6] The latter case occurred in Deschutes County, where two thirds of the patients described in this report became infected. By 1932, borreliosis had been recognized as endemic to 13 far-western states.

Transmission of endemic relapsing fever occurs by the bite of an argasid tick which harbors the spirochetes. The tick is always a species of *Ornithodoros: O hermsi* in the western United States and *O turicata* in the southwestern states. Borreliae have been isolated from *O parkeri* in the

western states, but this species has never been documented as a vector for relapsing fever. Ticks of this genus have a nearly painless bite, a short feeding time (1 to 20 minutes) and a tendency to nocturnal feeding.[7(p191)] *O hermsi,* like other species of *Ornithodoros,* are able to survive months or years without food and once infected with borreliae usually remain infective for life.

The disease appears more likely to occur in visitors to tick infested areas. As reflected by the patients in this series, these are generally young men traveling or working in heavily wooded areas during the summer months. This seasonal incidence has been noted previously with 66.4 percent of 253 cases in California occurring during July and August.[8] Lodging in poorly maintained cabins or other shelters in which ticks and their rodent hosts abide is a major factor in the acquisition of the disease. Recent outbreaks have been reported in other western states, including Colorado[9] and Washington.[3] The former involved 62 cases and is the largest known outbreak of tick-borne relapsing fever in the western hemisphere. In addition, the presence of active, endemic foci of relapsing fever in Colorado[10] and California[11] has been reconfirmed.

Excellent and comprehensive reviews on the clinical manifestations of borreliosis are available.[4,12] Several of the more common features, however, deserve reiteration.

Except for the relapsing nature of the disease, the clinical features are compatible with several illnesses that may or may not involve infection. The incubation period is approximately a week, but may be as brief as 72 hours. A history of tick-bite is confirmed in a minority of patients. The onset is characteristically sudden and typical symptoms include fever, rigors, severe headache and profound malaise. The patient may complain of intense myalgias, particularly in the lumbar region. Weakness and arthralgia may be present as well. Abdominal pain in the left and right upper quadrants is another common complaint. This pain may be associated with nausea, vomiting or diarrhea and may be severe. Respiratory symptoms include dyspnea and nonproductive cough.

The physical examination shows variable findings, but generally the temperature is higher than 39.5°C (103.1°F). Many patients have a rash which varies from a nonspecific macular eruption to classic rose spots or frank petechiae. Nuchal rigidity, without other meningeal signs, may be observed. Abdominal tenderness is common, but peritoneal signs are found only rarely. Splenomegaly is found by examination in slightly fewer than half of the cases,[12] and in this series was the most commonly mentioned physical finding after fever. Splenic tenderness may be present in the absence of overt splenic enlargement. Hepatic tenderness is common with or without associated hepatomegaly, which is noted in approximately 20 percent of cases. Tender lymphadenopathy is often dectected. Icterus is seen in about 40 percent of cases. Neurological changes most frequently involve an altered sensorium related to toxemia. Alteration in reflex and motor function may be present but is not common.

While the above description is nonspecific, the relapsing course of the disease should suggest the diagnosis in the absence of knowledge of previous exposure. Three quarters of the patients in this series with ascertained fever patterns had three or more febrile relapses. The pattern of pyrexial episodes, lasting from less than one day to about two weeks, alternating with afebrile asymptomatic periods lasting about a week, is classic for relapsing fever. The average duration of the initial attack is three to four days, and subsequent attacks are often somewhat shorter. Afebrile intervals vary in length between one and 60 days, although most last about a week. The mean number of relapses in a large series of cases was three, but up to 13 have been reported.[12] In the present series up to five relapses were common. Pyrexia terminates in a crisis, which is usually as abrupt as the onset of symptoms.

The relapsing character of the disease has been shown to be related to antigenic phase variation.[13] The *Borrelia* organism possesses the capability to adapt itself repeatedly to host antibodies by altering its antigenic profile. Each such alteration requires the host to mount a new immune response. The number of such adaptations is limited, and therefore the disease is eventually controlled by immune mechanisms.

The diagnosis should be considered in a patient with a history of a recent wilderness exposure, who has had two or three discrete episodes of high fever of abrupt onset and resolution associated with the first bout of fever. In only one of our patients was the peripheral blood smear examined expressly for *Borrelia* during the initial period of fever, and this was done because of historical information linking this patient to another person with known borreliosis.

The diagnosis can be confirmed by careful

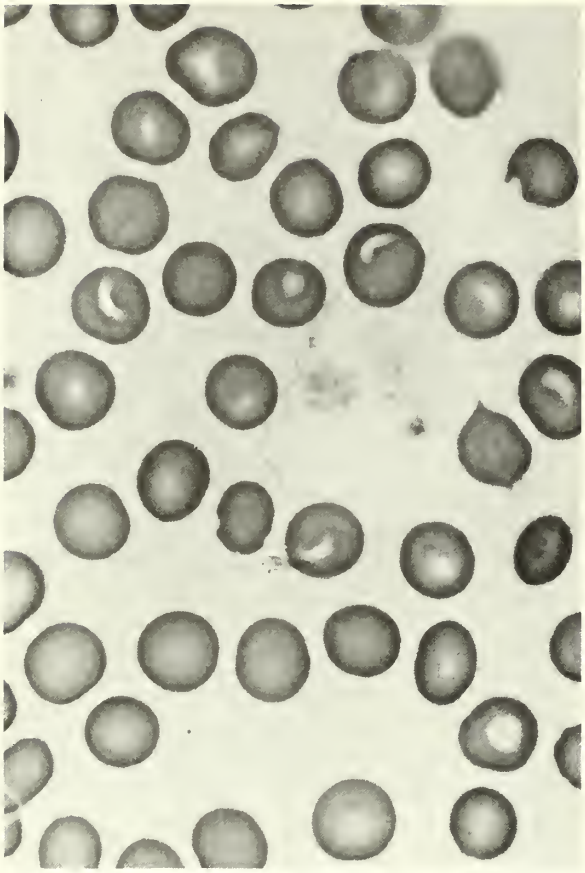

Figure 3.—Spirochetes on peripheral blood smear (Wright stain, reduced from 500× magnification).

examination of a Giemsa- or Wright-stained smear of peripheral blood (Figure 3) in which spirochetes will be found in approximately 70 percent of cases. The yield is increased by examination of serial blood smears, including thick and thin preparations. Evidence suggests that the organisms take refuge in the central nervous system, spleen, liver and bone marrow between attacks. (These organisms are almost never found on blood smears made during afebrile periods.) Dark-field examination of the blood may also be useful as may daily injections of the patient's blood specimens into laboratory mice. The spirochetes may then be seen in blood smears from the animal. Serologic tests are not generally of value in the diagnosis of relapsing fever.[7(p225)]

Other laboratory abnormalities include a mild normocytic-normochromic anemia, elevated levels of hepatocellular enzymes and hyperbilirubinemia. Study of coagulation times will often show multiple abnormalities, even in those patients without clinical evidence of bleeding. In louse-borne relapsing fever, prolongation of the prothrombin time and partial thromboplastin time has been observed, as have circulating fibrin monomers.[14,15] Platelet counts are usually low and range from 30,000 to 250,000 per cu mm in the louse-borne variety. Findings in case 1 show that these changes may also occur with tick-borne relapsing fever and that the abnormalities respond to treatment of the underlying disease.

The pathogenesis of the coagulation abnormalities may be related to a consumptive process initiated by endothelial damage caused by the spirochetes, or to release of factors which activate intravascular coagulation and fibrinolysis or perhaps to a combination of both.

The differential diagnosis depends to a great extent on the geographic locale and the history of activity and travel provided by the patient. Bacterial infections to be excluded include salmonellosis, meningococcemia, brucellosis and plague. Other spirochetal infections, including leptospirosis, and rat-bite fever should be considered along with rickettsial diseases such as typhus, Rocky Mountain spotted fever and Q fever. Viral agents, such as influenza virus and coxsackievirus, as well as members of the arbovirus group (for example, dengue or yellow fever) may cause similar syndromes. Colorado tick fever is also a potential source of confusion. Finally, features of malaria may develop in a very similar fashion. It is of interest that the diagnosis of borreliosis in two cases included in this report was made fortuitously during review of peripheral blood specimens for malarial parasites.

Three key points are important to note in considering a diagnosis of relapsing fever. First, relapsing fever does indeed occur in this country, especially in the western United States. Many of these cases are missed, probably because of the spontaneous recovery of most patients. The difficulty comes in placing this disease in the differential diagnosis of a febrile illness before the classic relapsing pattern of fever is apparent. Second, a bit of epidemiologic investigation can be very rewarding, as was shown in case 1. In this series, fewer than a third of cases were isolated, that is, unrelated to any other reported case. Third, the diagnosis, once thought of, is usually made easily by careful inspection of the peripheral blood smear.

The tick-borne disease is generally self-limited and has a mortality of only about 2 percent, mainly in infants and elderly patients. In keeping with the findings of other authors, the only deaths

in this series were those of a newborn infant and a 68-year-old woman. However, the morbidity is significant in terms of prolonged discomfort and disability to patients. It has been shown that an adequate course of antimicrobial therapy is effective both in terminating the current symptoms and in preventing relapses. The recommended therapeutic regimen is 500 mg of tetracycline taken orally four times a day for five to ten days. All patients in this series who were known to be treated with tetracycline responded well without relapse. Chloramphenicol is also effective if tetracycline is contraindicated or unavailable. Of note, however, is the case of the newborn infant who died with meningeal involvement. He was treated with chloramphenicol and penicillin but did not respond.[1]

Following treatment of tick-borne relapsing fever, recovery is typically rapid and complications are infrequent. Complications that have been described include iritis, iridocyclitis and a variety of focal neurological deficits. Pneumonia has been reported, and several patients in our series had a cough. Cardiac involvement has not been described in tick-borne relapsing fever; however, although undocumented, it is suggested by the course of the patient in case 2. Myocarditis has been described in louse-borne relapsing fever.[16] Hemorrhagic occurrences are common in reports of cases in Africa, but are rare in this country, occurring primarily in persons with laboratory evidence of severe coagulopathy. Abortion is frequent in pregnant women with relapsing fever. Intrauterine infection of the fetus is a rare complication which occurred in only one of the cases described in this series.

An additional complication is that of the Jarisch-Herxheimer reaction (JHR) which is characterized by elevation of temperature, aggravation of existing skin lesions and vasoconstriction followed later by hypotension. The JHR has an abrupt onset after initial treatment with antibiotics, and resolves without discontinuation of therapy. Its cause is thought to be related to release of endotoxin by borreliae.[17,18] Four patients in this series had this complication.

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Selection of Patients for Coronary Artery Bypass Operations

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Bypass operations have proved to be an effective treatment for advanced coronary artery disease. Randomized clinical trials have now shown that compared with medical treatment, bypass operations enhance survival in patients who have three-vessel disease or left main coronary stenosis. The goals of both medical and surgical treatment should be to improve a patient's quality of life, extend survival and reduce medical care costs. Preliminary data suggest that bypass operations may be less costly than medical treatment in patients with severe angina that requires repeated or prolonged stays in hospital.

In the last several years, the indications for coronary artery bypass operations have become clearer. This operation has proved effective in relieving symptoms of angina pectoris and can enhance survival in patients with severe forms of coronary artery disease.[1,2]

Goals of Treatment

Both medical and surgical treatment in the 1970's appear to have favorably altered the natural history of patients with symptomatic coronary artery disease.[3,4] In selecting either form of treatment, three goals should be pursued. These are to improve the patient's quality of life, extend survival and reduce medical costs.

Angina pectoris, along with other symptoms of ventricular dysfunction, impairs the quality of life in patients with coronary disease. Symptoms usually develop during emotional or exertional stress, when the oxygen demands of the heart are increased. Coronary artery obstructions involving up to 85 percent to 90 percent narrowing of arterial diameter will not impair myocardial blood flow at rest[5]; however, coronary artery stenotic lesions involving more than 40 percent to 50 percent narrowing of arterial diameter will impede flow during maximum exertion, when myocardial blood flow requirements can increase up to fourfold.[6] In addition to angina pectoris, symptomatic manifestations of exercise-induced ischemic ventricular dysfunction include complaints of "tiring easily," dyspnea on exertion and becoming easily fatigued. Exercise-induced ventricular dysfunction can be assessed by treadmill testing and by radionuclide techniques. On treadmill testing important indices of ventricular performance are the maximum duration of exercise (compared with that of healthy persons of the same age and sex and having the same physical activity status), and the maximum heart rate and blood pressure response.[7] Also, changes which occur in left ventricular wall motion and ejection fraction during

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ABBREVIATION USED IN TEXT
LMCAS=left main coronary artery stenosis

exercise now can be measured by noninvasive radionuclide techniques.[8,9] These tests can be used to evaluate the effect of medical and surgical treatment on ventricular performance. Both of these methods of treatment attempt to relieve angina pectoris and improve exercise performance, thereby enhancing the quality of a patient's life.

Coronary artery disease is the most common cause of death in the United States,[1] and thus, treatment must be directed towards improving survival as well. Bruschke and colleagues[10] established the natural history of patients with angiographically documented coronary artery disease in the 1960's, before the advent of beta-blocking agents and bypass procedures. They found that patients with left main coronary artery stenosis (LMCAS) and those with three-vessel disease had a relatively poor prognosis.

It has been estimated that the treatment costs of cardiovascular disease are now approximately $30 billion a year in this country.[11] One aspect of the controversy surrounding the coronary bypass procedure is its seemingly high cost, approximately $10,000 to $15,000 for each uncomplicated operation. The cost of this procedure, however, must be compared with the cost of medical treatment. Despite its expense, one can argue that a bypass operation may be more cost-effective than medical treatment in the long term, if it can prevent future hospital stays for unstable angina and alleviate the need to take medications. The cost for a hospital stay in a coronary care unit now ranges between $500 and $800 a day. The cost of daily medication and repeated doctor visits for patients who are not treated surgically also can be considerable. In this era of limited financial resources for health care, the third goal of surgical bypass procedures must be to reduce overall medical care costs as compared with alternative forms of treatment.

Comparison of Medical and Surgical Treatment

Quality of Life

It is now well established that bypass operations improve myocardial blood flow, and thereby myocardial oxygen supply, while medical treatment reduces myocardial oxygen demand.[1] Studies using animals have shown that a low-resistance (4 mm in diameter) saphenous vein bypass graft can supply upwards of 90 percent of the distal coronary blood flow when the diameter of the native proximal coronary artery has narrowed by more than 50 percent.[12] However, bypass grafts usually do not alter myocardial blood flow at rest, except to myocardium supplied by a poorly collateralized coronary artery with more than 85 percent to 90 percent stenosis.[5] But a patent bypass graft around a proximally obstructed coronary artery will restore coronary flow reserve, and can supply blood at a rate demanded by the heart when its workload is increased during periods of exercise and emotional stress. Approximately 400 to 600 ml of blood per minute will flow through an open saphenous vein that is attached to the aorta,[13] an amount which is more than sufficient to meet maximal myocardial blood flow demands.[6]

Bypass operations relieve angina and improve ventricular performance on exercise by increasing myocardial blood flow.[4,14] Nevertheless, some patients will experience symptomatic improvement although the bypass grafts are found to be occluded, presumably due to a placebo effect of the surgical procedure.[15] In rare cases, relief of angina may occur from operative infarction of the angina-producing myocardial segment rather than from myocardial revascularization[16]; however, the vast majority of patients who are asymptomatic after a bypass procedure have patent bypass grafts that supply previously ischemic myocardium.[4] Overall, up to 90 percent of patients have relief of disabling anginal symptoms after a bypass operation.[2]

Medical treatment, in contrast, relieves symptoms of angina pectoris by reducing myocardial oxygen demands, so that the need for oxygen does not exceed its supply (that is, the blood flow capabilities of the diseased coronary arteries).[17] With medical treatment approximately 50 percent of patients have some relief of disabling anginal symptoms.[18] There is no good evidence, however, that diet, exercise programs, or administration of nitrates or beta-adrenergic blocking agents can improve myocardial blood flow through fixed atherosclerotic coronary artery obstructive lesions.[17]

Propranolol, given in adequate dosages (up to 600 mg per day) can relieve symptoms of angina pectoris, but does not improve ventricular performance on exercise.[17,19] In a prospective randomized study, Guinn and Mathur[19] found that no significant changes occurred in the rate-pressure

product (a noninvasive indicator of myocardial oxygen consumption) with medical treatment, but a statistically significant improvement occurred in rate-pressure product in patients who had bypass operations. Patients who require large doses of propranolol for control of angina pectoris often complain of having a "lack of energy," reflecting the limitation on ventricular performance imposed by beta-adrenergic blockade. Sexual dysfunction, manifested by impotency or decreased potency, occurs in up to 50 percent of patients treated with propranolol.[20] This side effect, of course, will affect the quality of life in patients with symptomatic coronary artery disease who are treated medically with beta-blocking agents.

Randomized studies have uniformly confirmed that bypass operations are more effective in relieving symptoms of angina pectoris than medical treatment,[2,18] but it is not yet known how long coronary artery bypass grafts will last. Expertly placed, approximately 90 percent of saphenous vein coronary bypass grafts will remain patent during the first year following the operation, with an annual attrition rate of approximately 1 percent to 2 percent over the next several years.[1] While femoral-popliteal saphenous vein bypass grafts have been shown to last as long as 20 to 30 years, further follow-up of coronary bypass grafts will be necessary before long-term patency rates can be established.

Survival

Both bypass operations and medical treatment with long-acting nitrates and propranolol appear to improve survival in patients with multiple-vessel disease compared with the angiographically-defined natural history data reported by Bruschke and associates in the 1960's.[3,4,10] It has now been shown through randomized clinical trials that both symptomatic patients with left main coronary artery stenosis and those with three-vessel disease have improved survival with bypass operations as compared with medical treatment. In the Veterans Administration Cooperative randomized study (1976), bypass operations in patients with left main coronary stenosis, carried out with a 14 percent operative mortality, have been shown through patient follow-up to improve survival compared with medical treatment.[21] Operative mortalities of less than 2 percent are now being reported for bypass procedures in patients with left main coronary artery stenosis.[22] In the European randomized study, symptomatic patients with three-vessel disease have been shown to have a statistically significantly improved rate of survival after a bypass operation, carried out with a 3 percent mortality, compared with medical treatment.[23] In a large nonrandomized study, medical and surgical patients were closely matched retrospectively (by computer), using a large number of clinical, exercise, angiographic and quantitative ventriculographic variables. Results showed that bypass operations improved survival in patients with two-vessel disease and moderately impaired ventricular function.[24] Patients with single-vessel disease, however, have a very high rate of survival with either medical or surgical treatment.[1] Although not yet investigated by a randomized trial, patients with more advanced lesions in the left anterior descending coronary artery proximal to its first septal and diagonal branches may constitute a subgroup of patients with single-vessel disease for whom bypass operations may favorably influence survival.[25]

Medical Care Costs

In the long term, bypass operations actually may be a less expensive form of treatment than medical management in patients with symptoms of angina pectoris severe enough to require being in hospital. Collins and co-workers,[26] by comparing the frequency of hospital stays before and after bypass operations in 100 patients operated on consecutively at the Peter Bent Brigham Hospital, found that the hospital costs of bypass operations were amortized within 4.5 years. Other studies suggest that a substantial savings in hospital costs can be realized by operating on selected patients with severe coronary disease who, treated medically, are likely to require repeated stays in hospital because of failure to control symptoms.[27,28] However, data regarding hospital care costs of medical and surgical treatment are preliminary and require further study before firm conclusions can be made regarding the respective costs of medical and surgical treatment of patients with coronary artery disease.[1]

Selection of Patients

Relief of Angina Pectoris

The primary indication for a coronary bypass operation is, of course, to relieve symptoms of disabling angina pectoris unresponsive to adequate medical treatment.[29-31] While almost all physicians now accept this indication for a bypass procedure, wide latitude exists in interpreting what constitutes

"disabling" angina or "adequate" medical treatment. Some persons will feel disabled when anginal symptoms restrict their participation in recreational sports and impair their sexual activity, while others might not consider their lifestyle adversely affected until symptoms occur with more sedentary activities. Also, some cardiologists consider a trial of 80 to 160 mg of propranolol a day to represent adequate medical treatment, while others will prescribe up to 400 to 600 mg a day before declaring medical treatment a failure.

When patients with symptoms of angina pectoris can undergo a bypass operation with an operative mortality risk of 1 percent or less and a probability of symptomatic improvement of 90 percent or more,[2] the criteria of what constitutes "disabling" angina will most likely be interpreted more loosely to include a wide spectrum of lifestyles that are adversely affected by anginal symptoms, such as the inability to engage in professional athletics. It should be noted that optimal medical treatment may control anginal symptoms, but at the cost of side effects that leave a patient feeling "dull," tired or sexually impotent. Obviously, the surgical indications of "disabling" angina pectoris unresponsive to "adequate" medical treatment can be interpreted in a variety of ways by both patients and their physicians, and the competence and previous record of the surgical team to which the patient would be referred for a bypass operation must be considered as well.

Symptomatic patients with LMCAS and three-vessel disease should undergo bypass operations even if their symptoms can be controlled by medical treatment, because survival of these subgroups of patients is clearly improved with the procedure.[21,22] Some cardiologists and cardiac surgeons believe that symptomatic patients with two-vessel disease, particularly those with moderately impaired ventricular function, and patients with single-vessel disease involving more advanced stenosis of the left anterior descending artery proximal to its first septal branch should undergo bypass operations in lieu of medical treatment.[24,25,31] These indications, however, have not yet been validated by a prospective randomized study.

Unstable Angina

The term "unstable angina" includes a variety of clinical syndromes, defined primarily by the development of anginal symptoms at rest that are severe enough to require hospital care.[32] Patients with this condition are considered at risk for impending or extending myocardial infarction. Patients with recurrent angina at rest can be divided into three groups: (1) those whose symptoms can be controlled medically by physical and emotional rest in hospital and by administration of pharmacological agents (unstable angina); (2) patients whose symptoms are refractory to maximum inhospital medical treatment (preinfarction angina) and (3) those in whom angina occurs at rest shortly after a documented myocardial infarction (postinfarction angina). The term unstable angina has also been used by some physicians to denote either a new onset of angina of effort, or an increasing frequency and severity of symptoms of angina during exertion (crescendo or accelerating angina).[33] This last condition may constitute a fourth division of patients with unstable angina.

In our experience, less than 10 percent of patients with angina at rest have medically refractory preinfarction angina or postinfarction angina. The great majority of patients with recurrent angina at rest have uncomplicated "unstable angina," which responds to bed rest, administration of short- and long-acting nitrates and propranolol, and the correction of aggravating factors such as hypertension, anemia, thyrotoxicosis and tachyarrhythmias.

Four prospective randomized trials of medical and surgical treatment of unstable angina pectoris have been reported, and it is clear from these reports that bypass operations can be safely delayed in patients whose angina at rest responds to medical treatment.[33-36] Many of these patients, however, will eventually require a bypass procedure for control of symptoms. Although delay in operating does not appear to jeopardize survival or increase the likelihood of myocardial infarction, a high percentage of patients randomly chosen for medical treatment in the National Heart, Blood and Lung Institute study crossed over to have bypass operations because of recurrent unstable angina or continuing angina during physical exertion which adversely affected their life-style.[33]

The small percentage of patients in whom angina at rest is refractory to medical treatment (preinfarction angina) and those patients in whom postinfarct angina does not respond to medical treatment require immediate bypass operations when feasible (based on coronary angiographic findings and the status of ventricular function). Anginal chest pain and other manifestations of

ischemia, however, must first be controlled in order to minimize the risks associated with arteriography and bypass operations. Intra-aortic balloon pump counterpulsation effectively controls chest pain in patients with preinfarction angina and medically refractory postinfarct angina.[37-39] We believe that the safety of coronary arteriography and bypass operations can be enhanced when these patients are brought to the catheterization laboratory and the operating room in a stable condition, that is, without ongoing myocardial ischemia at rest. Intra-aortic balloon counterpulsation decreases myocardial oxygen consumption while increasing the myocardial oxygen supply by improving coronary blood flow and reducing stroke work[38]; thus, it can stabilize patients with medically refractory angina at rest and permit carrying out coronary arteriography and bypass procedures with a maximum degree of safety.[37,38]

Variant Angina

Patients in whom angina occurs at rest but not on exercise and in whom ST segment elevations occur (variant angina or Prinzmetal angina) often are found to have coronary spasm.[40] In patients without hemodynamically significant atherosclerotic coronary obstructions, a bypass operation is usually ineffective.[41]

Asymptomatic or Minimally Symptomatic Patients

Indications for coronary arteriography in patients with little or no chest pain are a previous myocardial infarction, an abnormal exercise test or a history of near-lethal arrhythmia.[42,43] Even if severe coronary disease is found on angiography, should asymptomatic patients undergo a coronary bypass operation? Although randomized studies have shown that bypass operations improve survival in *symptomatic* patients with three-vessel disease and LMCAS, these data should not necessarily be applied to asymptomatic patients who have coronary disease of equal severity. Natural history studies of patients with angina pectoris, however, have shown that the frequency and severity of anginal symptoms are poor predictors of survival; other clinical findings (such as hypertension,[44] abnormalities noted on electrocardiograms [ECG][45] and exercise-induced hypotension[46]), the number of diseased coronary vessels found on angiography and the status of ventricular function are much better predictors of survival.[10] Furthermore, symptoms of angina pectoris are an insensitive indicator of coronary heart disease. In only a third of patients who die of coronary heart disease do symptoms of angina pectoris ever develop, and it is not uncommon to have physiologically significant myocardial ischemia sufficient to impair one's quality of life without having anginal chest pain.[1] Some patients with physiologically significant coronary disease have dyspnea on exertion, considered an angina equivalent, or simply have less energy and complain of "tiring easily."

Nevertheless, one would not expect that for patients with coronary disease who are asymptomatic and who feel well a coronary bypass operation will improve their quality of life. And there are no data as yet that survival is improved in patients who have LMCAS or three-vessel disease but who do not have symptoms of angina. Results of coronary arteriography may show evidence of anatomic disease which, however frightening in appearance, may not pose any physiological significance with regard to restricting myocardial blood flow. If surgical treatment is considered in an asymptomatic patient it must be first shown that the angiographically documented coronary lesions are of physiological significance, that is, that they restrict coronary flow reserve.[47] Available techniques, notably treadmill testing and rest and exercise radionuclide cineventriculography, should be used to document the presence of exercise-induced ischemic ventricular dysfunction. Impairment in myocardial perfusion can also be assessed clinically by thallium 201 exercise scintigraphy.[48] Asymptomatic or minimally symptomatic patients in whom LMCAS is more than 50 percent or in whom three-vessel disease involves more than 70 percent constriction may be considered candidates for a bypass operation by aggressive cardiologists and cardiac surgeons.[31,49] However, it is important to obtain evidence of physiological impairment in ventricular performance in such patients. No definitive evidence exists to support the role of bypass operations in asymptomatic patients with coronary artery disease, but such an approach is being increasingly favored in patients with LMCAS and three-vessel disease who have positive treadmill tests.[30,31]

Uncomplicated Acute Myocardial Infarction

Although several uncontrolled clinical studies have been reported supporting the role of immediate bypass surgery for patients with acute uncomplicated myocardial infarction,[50] this indication for a bypass procedure is not accepted by

most cardiologists and cardiac surgeons. It is difficult to even make a diagnosis of myocardial infarction when a patient with chest pain is rushed to the operating room before enzymatic and ECG changes occur that can document this condition. Experiments on animals suggest that early reperfusion after coronary occlusion sometimes can be deleterious, by extending infarct size due to postreperfusion myocardial hemorrhage.[51-53] New techniques of intracoronary administration of nitroglycerin and the use of streptokinase in the management of acute myocardial infarction are also being investigated.[54]

Postinfarction Angina

As previously discussed, a patient in whom angina develops shortly after an acute myocardial infarction that does not respond to pharmacological management should be considered for prompt bypass operation after the condition has been stabilized with intra-aortic balloon counterpulsation.[55] Such patients often do very well, with an operative mortality now in the range of 5 percent to 10 percent.[56]

Mechanical Complications of Acute Myocardial Infarction

Four mechanical complications can occur within the first two weeks after an acute myocardial infarction: (1) pure left ventricular power failure (cardiogenic shock), (2) papillary muscle rupture (or dysfunction), (3) perforation of the ventricular septum and (4) rupture of the ventricular free wall. Concomitant bypass procedures may be carried out in patients operated on for mechanical complications of acute myocardial infarction; indeed, a bypass operation alone may be done in an attempt to reverse postinfarction cardiogenic shock.[57] Bypass operations for pure left ventricular power failure complicating myocardial infarction is associated with a high operative mortality, and is not widely practiced. The value of bypass operations in association with repair of a postinfarction septal defect or mitral replacement for papillary muscle dysfunction is uncertain.[57,58]

Life-Threatening Ventricular Arrhythmias

As yet there is no evidence that bypass operations prevent exercise-induced ventricular arrhythmias.[59] So far only a small number of patients have been reported who have had bypass operations after being successfully resuscitated from an episode of sudden death. Investigators have not accumulated sufficient data to define the role of bypass operations for patients surviving sudden death or for those with life-threatening ventricular arrhythmias.[60-62] Uncontrolled studies and anecdotal reports to date have been disappointing with regard to the potential value of bypass operations in controlling ventricular arrhythmias.

Other Considerations

Coronary Anatomy

The feasibility of bypass grafting is determined by the size of the coronary artery and the degree of distal disease. Approximately 80 percent to 90 percent of coronary arteries larger than 1 mm in diameter with proximal narrowing of more than 50 percent (the minimal degree of constriction necessary to affect coronary flow reserve) can be grafted. Coronary artery disease is usually classified as one-, two- or three-vessel disease or LMCAS, but it is important to realize that coronary anatomy has a fair degree of variability, and statements regarding the number of diseased vessels often do not clearly indicate the true severity of coronary disease.[63] Not every patient's epicardial coronary arteries consist of three vessels equal in size and blood flow. For example, a person with two-vessel disease involving a small anterior descending and a small right coronary artery in the presence of a large, nondiseased circumflex artery will not have anatomic findings that reflect two-vessel disease. In contrast, a right coronary artery or circumflex artery may be sufficiently dominant so that a proximal stenosis in the vessel is equal in its dysfunction to two-vessel disease. The relative portion of left ventricle in jeopardy is more crucial than whether a person has one-, two- or three-vessel disease.

Ventricular Function

The amount of viable myocardium present, as determined by contrast or radionuclide ventriculography, is an important factor in selection of patients for bypass operations. Patients with a low ejection fraction and a large end-diastolic volume may benefit from the procedure, but will be at increased operative risk. Patients with impaired resting ventricular function who have been shown to have transiently improved wall motion after nitroglycerin or after a premature ventricular beat are more favorable candidates for bypass operations.[64-66] Nevertheless, even patients with

very low resting ejection fractions and who are disabled by symptoms of angina pectoris, may benefit from bypass operations with a relatively low operative risk.[1]

Status of Vital Organ Function

Although not well defined, associated carotid artery disease increases the risk of a cerebral vascular accident during or shortly after coronary bypass operations.[63] Carotid endarterectomy has been done before or concomitant with bypass operations in an attempt to minimize the risk of neurological complications when carotid disease coexists.[67] Patients with advanced pulmonary disease can safely undergo bypass operations by means of a median sternotomy incision, with a low risk of pulmonary complications.[68] Also, patients in chronic renal failure or who have had a kidney transplant have undergone bypass operations successfully.[69]

Age

In the early 1970's bypass operations were usually not done in patients over 70 years of age because of the increased risk of cardiac operations in such persons. Many surgical teams now carry out bypass operations in patients who are more than 70 or 80 years old, with only a slightly increased operative risk.

Religious Convictions

A religious sect, the Jehovah's Witnesses, does not permit its members to receive blood transfusions. Some surgical teams will carry out bypass operations without resort to blood transfusions, and have done so with remarkably good results.[70,71] Therefore, this religious proscription is not necessarily a contraindication to a bypass operation.

The Role of Percutaneous Transluminal Coronary Angioplasty

Percutaneous transluminal coronary angioplasty, in which an expansile balloon, mounted on a selective coronary artery catheter, is used to dilate stenotic coronary arteries, is applicable to only a small subgroup of patients with coronary artery disease. This group includes patients with single-vessel disease who have a proximal, discrete, noncalcified, concentric obstructive lesion.[72] The results of transluminal angioplasty carried out in 205 patients at four centers with personnel who have the most experience doing the operation, indicate that the morbidity and mortality of this procedure exceeds that of coronary bypass operations in this category of patients.[72] Indeed, emergency bypass operations were required in ten of these patients, and it is recommended that centers which carry out this procedure have a surgical team on standby for any emergent complications that may occur.[73] Until further data become available it would appear that percutaneous transluminal coronary angioplasty has not yet become a clinically viable alternative to medical or surgical treatment.

Summary

Although a palliative treatment, the coronary artery bypass procedure has proved to be of great value in the treatment of patients with advanced coronary artery disease. Following on a long history of discredited operations for angina pectoris, the efficacy of this procedure has become firmly established over the first decade of its use, and the indications for a bypass operation have now become better defined.

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Clinicopathologic Conference

Discussants

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Refer to: Sherman JL, Schwabe AD, Pagani JJ, et al: A 21-year-old woman with fever and pancytopenia, UCLA School of Medicine (Clinicopathologic Conference). West J Med 133:218-225, Sep 1980

A 21-Year-Old Woman With Fever and Pancytopenia

Report of a Case

JOHN L. SHERMAN, MD:* A 21-year-old Mexican-American woman was admitted to the University of California, Los Angeles (UCLA) Hospital because of fever and malaise. She felt well until 2½ weeks before admission, when she first noted headache, malaise and extreme fatigue. Several days later her temperature rose to 40.0°C (104°F), but this was not accompanied by chills or sweating. Five days later a cough developed, which produced small amounts of clear sputum, and she was treated on successive occasions with ampicillin, penicillin and tetracycline. A leukocyte count of 2,700 per cu mm was noted. Five days before admission a spontaneous ecchymosis appeared under her left eye and gingival bleeding occurred when she brushed her teeth.

The patient had had her tonsils and adenoids removed at age 4 and an appendectomy at age 7. At the time of admission she was taking no medications, did not smoke, drink or use drugs. She lived with her family, all of whom were in good health, and she visited Ensenada, in northwest Mexico, with her family regularly. Her aunt had died of a "cancer of the lymph glands," and her grandfather (with whom she did not live) had been successfully treated for tuberculosis four years earlier. She worked as a playground supervisor, and had a healthy cockatoo as a pet. She said that she had had no sexual contacts.

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On admission, her temperature was 37.3°C (99.1°F), pulse 100 beats per minute, respirations 20 per minute and blood pressure 110/20 mm of mercury. On examination the patient was well developed, well nourished, alert and appeared in no distress; head and neck were normal, and the chest was clear. A cardiac examination showed a grade 3/6 systolic ejection murmur at the left sternal border radiating to the pulmonic area. The abdomen was flat, liver was 8 cm in span to percussion, and no spleen or masses were palpated. Ecchymoses were noted over both legs. Findings of a neurological examination were normal. Adenopathy (0.5 to 1.0 cm) was noted in the posterior cervical, occipital, axillary and inguinal regions bilaterally.

Analysis of urine showed proteinuria and moderate ketones, and three to four leukocytes and rare erythrocytes per high-power field. The hematocrit was 27.5 percent, the leukocyte count was 830 per cu mm, with 60 percent segmented neutrophils, 36 percent lymphocytes and 4 percent monocytes. The platelet count was less than 80,000 per cu mm, with occasional large forms, and the erythrocyte sedimentation rate was 42 mm per hour. Urea nitrogen value was 4 mg per dl, and sodium was 140, potassium 3.3, chloride 108 and bicarbonate 29 mEq per liter. Alkaline phosphatase was 77 units per liter; amylase was 56, total bilirubin 0.7 and calcium 8.6 mg per dl. Lactic dehydrogenase (LDH) was 934, serum aspartate aminotransferase (SGOT) 355 and serum alanine aminotransferase (SGPT) 326 units

per liter; uric acid was 1.2 mg per dl. The prothrombin time was 11.6 seconds, the partial thromboplastin time was 34.9 seconds. An x-ray study of the chest showed no abnormalities, and a mononucleosis spot test was negative.

A bone marrow examination was done, showing hypocellularity without diagnostic changes. Cultures for bacteria, fungi and tuberculosis were negative. Titers for Epstein-Barr virus, cytomegalovirus, toxoplasmosis, Q fever, leptospirosis, cocci and heterophile antibodies were negative. Brucella titer and febrile agglutinins were all negative. Tests for antinuclear antibodies, lupus erythematosus, hepatitis-associated antigen, rheumatoid arthritis and fluorescent treponemal antibodies were also negative. A VDRL test was positive at 1:2. A direct Coombs test was positive and an indirect Coombs test was negative. The folate level was normal and vitamin B_{12} level was 5,340 pg per ml (range 330 to 1,025). The total protein was 6.5 and albumin 4.2 grams per dl; the total 24-hour urine protein was 370 mg per liter; urine hemosiderin and a sucrose hemolysis test were negative. The following cultures were negative: three cultures of urine specimens for C&S (culture and sensitivity) and three for acid-fast bacillus (AFB); eight cultures of blood specimens; three cultures of stool specimens for C&S and three for ova and parasites. A serum leukocyte alkaline phosphatase score was 79 (range 21 to 58). Skin tests for streptokinase-streptodornase, mumps, and coccidioidomycosis, as well as the tuberculin skin test using purified protein derivative (5 TU PPD) were all negative.

On the fourth hospital day, SGOT was 104, SGPT 120 and LDH 818 units per liter; findings of a repeat x-ray study of the chest were normal. A liver-spleen scan showed no abnormalities.

The patient continued to have daily fever spikes to 39.8°C (103.6°F) associated with tachycardias to 120 beats per minute. By the ninth hospital day, the SGOT was 67, SGPT 53 and alkaline phosphotase 74 units per liter. The leukocyte count was 2,400 per cu mm, hematocrit 23.1 percent, and platelet count 45,000 per cu mm. Five days later, the leukocyte count had fallen to 549 per cu mm with 62 percent segmented neutrophils, the anti-DNA was 12 percent, the total hemolytic complement was 23 hemolytic units (range 20 to 50), the beta-1-C complement was 67 mg per dl (range 80 to 160), a gallium scan was nondiagnostic and malaria smears were negative. Findings of lumbar puncture, barium enema and upper gastrointestinal tract studies, intravenous pyelogram and echocardiogram were all normal. A skin biopsy was nondiagnostic.

Figure 1.—Lymphangiogram showing enlarged, foamy pelvic and aortic lymph nodes.

Fevers with spikes as high as 41°C (105.8°F) persisted. On the 35th hospital day findings of an indium-bleomycin scan were normal; however, a bone scan showed increased nucleide accumulation in the left knee, left femur and left fibula. A lymphangiogram (Figure 1) showed enlarged, foamy appearing pelvic and aortic lymph nodes and widening of the superior mediastinum with increased density consistent with lymphoma. An abdominal ultrasound test showed a 2- by 3-cm retroperitoneal mass on the right side, 4 cm above the umbilicus.

On the 41st hospital day, biopsy of two large left inguinal lymph nodes was done. Pathologic examination showed no diagnostic changes, and smears and cultures for bacteria, AFB and fungi were negative. On the 46th day, an x-ray study of the chest (Figure 2) showed diffuse, bilateral, reticulonodular infiltrates. Analysis of arterial blood gases while the patient breathed room air showed a pH of 7.45, carbon dioxide pressure (P_{CO_2}) of 40.5 torr and oxygen pressure (P_{O_2}) of 90 torr. The chest was clear on examination, and sputum smear for AFB was negative. The

SGOT was 13, SGPT 13 and alkaline phosphatase 86 units per liter. On the 49th hospital day, a diagnostic surgical procedure was carried out.

Clinical Discussion

ARTHUR D. SCHWABE, MD:* The young woman presented with four symptoms: cough, fatigue, headache and malaise (Table 1). A workup directed at finding the cause of the cough, including repeated examinations and cultures of the sputum as well as roentgenograms of the chest, failed to be conclusive. The other three symptoms suggest an acute or chronic illness, but are too nonspecific to warrant any speculations at this point.

A prominent feature of the illness was a persistent fever with temperatures as high as 41°C (105.8°F), but without shaking chills or diaphoresis. A fever of such long duration indicated that besides a variety of infections we should consider a malignant condition such as Hodgkin disease, hypernephroma or sarcoidosis. Nolan and Klatskin[1] emphasized many years ago that fever may be a prominent feature in more than 40 percent of cases of sarcoidosis. However, although active granulomatous inflammation and pronounced systemic involvement have been suggested as being responsible for the fever in sarcoidosis, a definite relationship has not been established.

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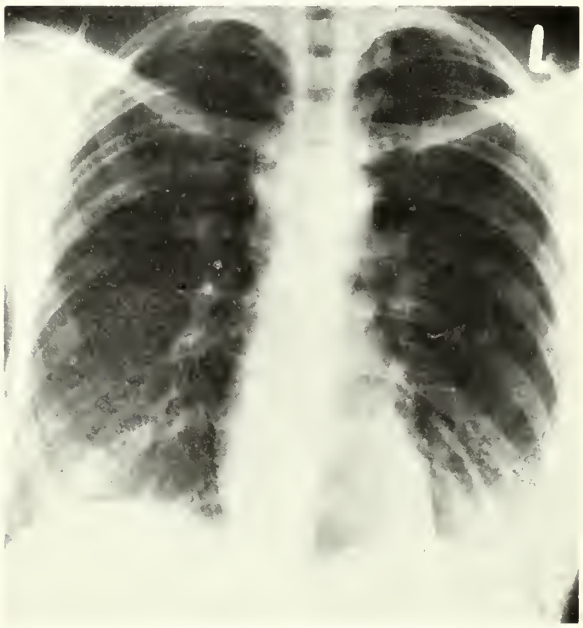

Figure 2.—Posterioanterior roentgenogram of the chest on the 46th hospital day, showing diffuse, bilateral, reticulonodular infiltrates.

TABLE 1.—*Clinical Features*

Symptoms	*Physical Findings*
Cough	Bleeding
Fatigue	Fever
Headache	Lymphadenopathy
Malaise	Systolic murmur

Our patient was found to have generalized lymphadenopathy, including enlargement of mediastinal, periaortic and pelvic nodes. This finding also raises a host of diagnostic possibilities: chronic infections, lymphomas, sarcoidosis and even systemic lupus erythematosus may present with generalized lymphadenopathy. A grade 3 systolic ejection murmur was noted on admission, but received no further comment in the remainder of the protocol. In a febrile patient with significant anemia, we can assume that this is a flow murmur related to increased blood flow. The patient also had evidence of bleeding, specifically gingival bleeding and ecchymoses of the face and lower extremities. However, bleeding manifestations did not seem to be a problem during the remainder of her long hospital stay. We know from the subsequent workup that she had mild to moderate thrombocytopenia and that large platelets were visible on peripheral smears. Such large platelets are usually indicative of immaturity. Because the prothrombin and partial thromboplastin times were normal and no other coagulation studies were done, we have to assume that the bleeding manifestations were due to quantitative or, more likely, qualitative platelet defects.

The protocol also states that the patient had a healthy pet cockatoo. Birds, particularly parrots and parakeets, may transmit psittacosis, toxoplasmosis and salmonellosis.[2] Psittacosis can be eliminated because of the absence of evidence of pneumonitis, the prolonged course and the failure to respond to tetracycline and penicillin. Toxoplasmosis can also be ruled out by the absence of uveitis and hepatosplenomegaly, as well as the failure to detect this infection by serologic and histologic methods. Finally, a *Salmonella* infection manifested as either paratyphoid or typhoid fever may very occasionally occur without any significant gastrointestinal symptoms. However, the negative cultures and serologic studies do not justify any serious consideration for such an infection. The patient was of Mexican ethnic background and had traveled to Mexico frequently; therefore, amebiasis must be considered. Intestinal amebiasis can be dismissed due to the absence of

diarrhea and negative findings on examination of stool specimens. An amebic abscess of the liver seems unlikely because of the prolonged course of illness and the normal liver scan. Thus, we can conclude that the history and physical findings provide very little information with which to focus on any single diagnostic entity. We will now review the patient's roentgenograms.

JOHN J. PAGANI, MD:* Findings on the roentgenogram of the patient's chest at admission were within normal limits. On the 30th hospital day, a repeat roentgenogram showed right-sided paratrachial and azygos node enlargement. The lung fields show some nonspecific increased reticular markings. On the 46th hospital day (Figure 1), the adenopathy was noted again, with the suggestion that the lung markings had become a bit more prominent. A lymphangiogram (Figure 2) showed prominent lymphatic channels with some displacement and lateralization of the lymphatic ducts during the early filling phase. The filling phase showed a process involving all of the lymph nodes visualized, with hyperplasia and enlargement of all of the nodes, but with the capsules intact. The hyperplastic nodes showed decreased concentration of the dye but uniform filling.

DR. SCHWABE: The lymph nodes were described in the radiology report as having a "foamy" appearance. Does this description suggest any specific process?

DR. PAGANI: Classically, in a lymphoma the lymph nodes are described as foamy; however, I am not certain that foamy is the right word to describe the lymph nodes in this case because they appeared of normal consistency but were enlarged and hyperplastic, while the sinusoids within the lymph nodes were intact. In the classic description of a lymphoma, there is disruption of the internal structure of the lymph nodes, which gives them a foamy appearance.

DR. SCHWABE: I conclude from your comments that the findings on the lymphangiogram were nonspecific. This could be consistent with lymphoma, infection or infiltration of any sort.

DR. PAGANI: That is correct.

DR. SCHWABE: We will next examine the other laboratory data for any clues regarding the nature of this febrile illness. The level of blood urea nitrogen (BUN) was low on admission and continued to be so throughout the patient's stay in hospital. Low BUN levels to a gastroenterologist usually indicate decreased synthesis due to severe liver disease. Although initially the levels of the transaminases and lactic dehydrogenase were elevated, I see no evidence of significant liver disease. The BUN may also be depressed if the protein intake is low or if proteolysis is spared by continuous glucose infusions. The moderate ketosis on admission may reflect a low caloric intake before admission and, subsequently, the multiple diagnostic studies may have further curtailed her intake. In addition, I suspect that she received intravenous glucose infusions throughout her hospital course. The significance of the low BUN is open to question, but it is clearly not related to significant liver disease.

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TABLE 2.—*Some Causes of Hypouricemia*

Decreased formation of urate
Liver disease
Xanthinuria
Xanthine oxidase inhibition by drugs
Increased renal clearance of urate
Fanconi syndrome
Carcinoma
Cystinosis
Nephrotic syndrome
Wilson disease
Syndrome of inappropriate antidiuretic hormone (ADH) secretion
Acute intermittent porphyria
Carcinoma
Central nervous system disorders
Hodgkin disease
Tuberculosis
Miscellaneous
Drugs (such as vitamin C and ticrynafen)
Hypercalciuria
Liver disease

The serum uric acid level on admission was 1.2 mg per dl and remained low throughout her hospital course. As clinicians we are accustomed to finding and explaining elevated levels of serum uric acid. Hypouricemia is considerably less common. A list of causes of this condition is given in Table 2. In general, it has been shown that hypouricemia can result from decreased production of urate or increased renal excretion of uric acid.[3-5] Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine and, in turn, of xanthine to uric acid. Therefore, xanthine oxidase deficiency as seen in liver disease or xanthinuria, as well as xanthine oxidase inhibition by drugs (such as allopurinol), may result in decreased

TABLE 3.—*Major Causes of False-Positive Tests for Syphilis*

Autoimmune disorders (such as systemic lupus erythematosus)
Chronic liver disease
Hyperglobulinemia
Infections (bacterial, viral)
Leprosy
Lymphoma
Malaria
Narcotic addiction
Vaccinations
Pregnancy
Thyroiditis

TABLE 4.—*Diagnostic Considerations of Aplastic Anemia*

Infections	Tumors
Brucellosis	Hodgkin disease
Cytomegalovirus infections	Malignant histiocytosis
Histoplasmosis	Miscellaneous
Infectious mononucleosis	Drugs
Q fever	Sarcoidosis
Toxoplasmosis	Systemic lupus erythematosus
Tuberculosis	
Typhoid fever	
Viral hepatitis	

production of urate. Increased renal excretion of uric acid may occur in association with generalized or isolated renal tubular defects, as in the Fanconi syndrome and liver disease, respectively. Recently, there has been renewed interest in the association of hypouricemia and the syndrome of inappropriate antidiuretic hormone (ADH) secretion.[5] The latter may accompany Hodgkin disease, acute intermittent porphyria, tuberculosis and other disorders. Finally, increased renal excretion of urate and resulting hypouricemia may occur with lymphomas or carcinomas, and after ingestion of a variety of drugs, including ticrynafen and vitamin C. Levels of the three serum enzymes SGOT, SGPT and LDH, were moderately elevated on admission, but gradually returned to normal. Though possibly suggesting transient liver damage, it must be stressed that these enzymes are widely distributed in the tissues and elevations are not sufficiently specific to focus on a single diagnostic entity.

Elevated levels of leukocyte alkaline phosphatase may be found in association with stress, infection, leukocytosis, leukemoid reactions, myeloproliferative disorders and, less commonly, with Hodgkin disease.

Another interesting, though not very specific, laboratory abnormality was an elevation of the serum vitamin B_{12} level. High B_{12} levels may be seen in all types of liver infections, as well as in active cirrhosis, hepatic tumors and pyeloproliferative disorders. It should be remembered that the patient may have recently received an injection of vitamin B_{12} for "tiredness" by a well-meaning physician.

A positive VDRL test at low titer coupled with a negative fluorescent treponemal antibody (FTA) absorption test indicates a false-positive test. Major causes of false-positive tests for syphilis listed in Table 3 include many acute or chronic illnesses. This laboratory abnormality does not bring us much closer to a solution of this case.

We will next examine the most significant and persistent laboratory findings—pancytopenia and hypocellular marrow (Table 4). Hodgkin disease and sarcoidosis deserve serious consideration, because they may both present with aplastic anemia as well as generalized adenopathy and fever. Systemic lupus erythematosus should be mentioned, but cannot be seriously entertained in the absence of arthritis, polyserositis and negative serologic test findings. Of the infections with these hematologic findings we can eliminate all but viral hepatitis[6,7] and miliary tuberculosis.[8,9] Aplastic anemia following viral hepatitis has been described repeatedly in the literature. It tends to occur in young persons, usually below the age of 25 years. It does not correlate with the severity of the hepatitis, appearing as the hepatitis resolves. Thus, it may not be apparent for weeks or months after the patient has recovered from the acute illness. However, in this case the prominent lymphadenopathy, mild and transient elevation of enzyme levels and the timing of the aplastic process make viral hepatitis an unlikely possibility. Three disorders, Hodgkin disease, sarcoidosis, and miliary tuberculosis can be supported by the clinical features and most of the laboratory evidence, including the aplastic anemia, skin test anergy and positive Coomb test[10] (Table 5). Are there any clues that favor one of these entities over the other two?

Thus far, I have not mentioned the persistence of three to four leukocytes and an occasional erythrocyte in the urine specimens. Pyuria may be found in Hodgkin disease and sarcoidosis, particularly if there is a secondary infection. Both of these entities rarely may be accompanied by a membranous or proliferative glomerulonephritis, a complication not supported by the sparcity of urinary sediment in this case. In miliary tubercu-

losis, however, pyuria is frequently observed. The abnormalities seen on the x-ray studies of the chest also favor miliary tuberculosis. In classic sarcoidosis hilar adenopathy and discrete sentinel-type nodes generally are found. In neither sarcoidosis nor Hodgkin disease should the findings of roentgenograms of the chest change so rapidly with appearance of bilateral diffuse reticulonodular infiltrates, as was reported on the 46th hospital day. For all these reasons, I make a diagnosis of miliary tuberculosis.

I would like to reconsider the hematologic findings. In 1974 Cameron[9] summarized the abnormalities observed in the peripheral blood smear and the bone marrow in miliary tuberculosis. As shown in Table 6, tuberculosis can mimic almost any hematologic disorder. In struggling for a solution to this case I was reminded of a statement from the literature that tuberculosis is one of the most commonly incriminated conditions in cases of cryptogenic fever, yet is the most difficult to convict; nevertheless, it should always be considered.

What should be done to confirm the diagnosis? It should be noted that biopsies of the inguinal lymph nodes are notoriously unreliable, particularly if there is uncertainty about their involvement in the pathological process. I think a surgical bone marrow biopsy and culture would have been my initial procedure of choice.[11] A liver biopsy could be done, but in view of her thrombocytopenia I would have been concerned about the possibility of bleeding. Another approach could be an exploratory laparotomy and excision biopsy of one or more of the lymph nodes from the retroperitoneal area. Incidentally, the 2- by 3-cm retroperitoneal mass on the right side, which was detected by abdominal ultrasound testing, was probably a group of lymph nodes. I believe that careful examination and culture of any of these tissue specimens will confirm the diagnosis of miliary tuberculosis.

EDWARD D. CRANDALL, MD:* Would you consider doing a transbronchial lung biopsy as a way of establishing a diagnosis in this case?

DR. SCHWABE: Yes, that would be another approach to this case.

MARTIN J. CLINE:† I agree that tuberculosis is very high on your list, but I do not think that a surgical bone marrow biopsy would be a very good way to make that diagnosis. Even in miliary tuberculosis, you would be fortunate to see granulomas. We reviewed our case records here at UCLA, and we have never had a positive bone marrow culture for tuberculosis.

HARRISON J. L. FRANK, MD:‡ Did you ever consider making an empirical decision to begin antituberculous therapy earlier in the patient's hospital course?

DR. SHERMAN: We resisted this temptation frequently, believing that obtaining a positive diagnosis before beginning therapy was very important.

GREGORY P. SARNA, MD:§ I wonder if there were two processes going on, because if miliary tuberculosis is suspected as the entire cause of the patient's condition, would you not expect the liver function abnormalities to improve spontaneously?

DR. SCHWABE: Fluctuating changes in liver en-

TABLE 5.—*Laboratory Abnormalities and Correlation With Three Diagnostic Possibilities*

	Hodgkin Disease	*Sarcoidosis*	*Miliary Tuberculosis*
Anergy	+	+	+
Bone marrow	+	+	+
Lymphadenopathy	+	+	+
Hypouricemia	+	+	+
Pancytopenia	+	+	+
Positive bone scan	+	+	+
Positive Coomb test	+	+	+
Positive VDRL test	+	+	+
Pulmonary infiltration	+	+	+
Serum vitamin B_{12} elevation	+	+	+
Pyuria	−	−	+

TABLE 6.—*Hematologic Changes Associated With Miliary Tuberculosis**

Peripheral Blood	*Bone Marrow*
Anemias	Hypercellular
Aplastic	Hypocellular
Hemolytic (positive Coomb test)	Myelofibrotic
Hypochromic	Megaloblastic
Macrocytic	"Leukemic"
Normocytic	"Immature"
Agranulocytosis	"Erythroblastic"
Eosinophilia	Plasmacytic
Leukemoid reactions	Lymphocytic
Polycythemia	
Thrombocytopenia	
Pancytopenia	
Dysproteinemia	

*Modified from Cameron, SJ.[9]

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zymes are not unusual in miliary tuberculosis, and liver function tests might be entirely normal while liver biopsy specimens show evidence of tuberculosis. I think that this is quite compatible with that diagnosis.

Figure 3.—Photomicrograph of a liver biopsy specimen obtained at laparotomy, showing a cluster of three noncaseating granulomata. (Hematoxylin-eosin stain, reduced from magnification ×100.)

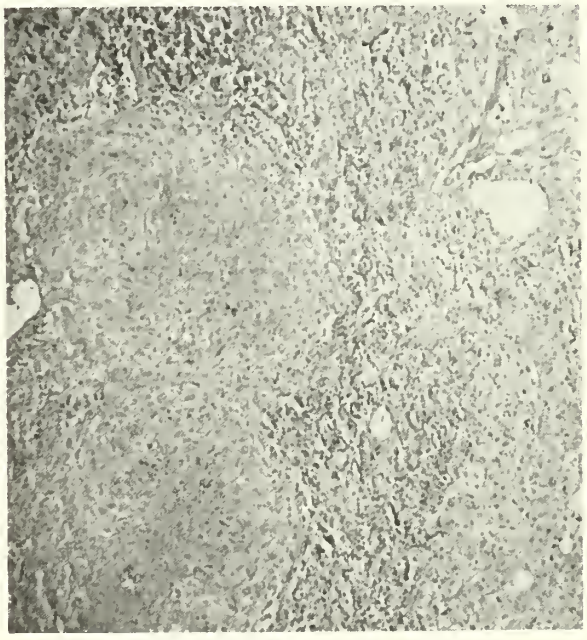

Figure 4.—Photomicrograph of a lymph node specimen obtained at laparotomy, showing multiple granulomata with central caseation necrosis. (Hematoxylin-eosin stain, reduced from magnification ×125.)

SHERMAN M. MELLINKOFF, MD:* The liver is peculiarly resistant to tuberculosis, and in Arnold Rich's book on tuberculosis several patients are described who died of miliary tuberculosis with healed tubercles in the liver.[13]

Discussion of Pathology

FREDRICK W. GILKEY, MD:† First, it should be noted that an inguinal lymph node biopsy study is not necessarily inappropriate. In one series[12] 16 of 22 such biopsies were diagnostic. Therefore, one should not hesitate to carry out an inguinal lymph node biopsy if that is the largest or most readily accessible lymph node, except perhaps in the presence of ongoing infection of the groin or lower extremities.

An exploratory laparotomy was carried out, at which time a liver biopsy and excision of abdominal lymph nodes were done. The liver (Figure 3) contained three noncaseating granulomata in a cluster. Giant cells were present. The lymph nodes (Figure 4) contained many caseating granulomata. The routine Ziehl-Neelson stain for acid-fast bacilli was negative; but, because the histologic findings were so typical of tuberculosis, the stain was repeated after tylene-peanut oil deparaffinization and overnight incubation. This process enhances the sensitivity of the stain which, in this case, showed scattered tubercle bacilli.

DR. SHERMAN: When x-ray studies of the chest first showed a diffuse reticular pattern four days before the operation, sputum specimens for acid-fast bacilli were obtained. Though the smears were negative, five weeks later the cultures were positive for *Mycobacterium tuberculosis*. Therapy with isoniazid (INH), ethambutol and rifampin was begun, and the patient rapidly defervesced and was discharged ten days later. Six months later the pancytopenia had resolved completely, but hepatitis B surface antigen-positive hepatitis developed; treatment with INH was discontinued. Seven months later, all antituberculous chemotherapy was stopped, and the platelet count at this time was 28,000 per cu mm. Findings of multiple serologic tests for collagen vascular diseases were negative. Two months later, however, the patient was readmitted with headaches, diarrhea, fever and chills. A complete blood count showed 1,100 leukocytes and a platelet count of 25,000 per cu

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†Chief Resident and Adjunct Professor of Pathology.

mm. After another extensive hospital stay all cultures were negative, and a decision was made empirically to begin therapy. The regimen included INH, ethambutol, streptomycin and prednisone, with immediate lysis of fever. At present, the patient is feeling well, although antiplatelet antibodies, splenomegaly and a pronounced positive antinuclear antibody reaction have developed. She continues to receive INH, ethambutol and low-dose prednisone.

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Early Signs and Symptoms of Breast Cancer

WITH REGARD TO the signs and symptoms referable to the breast, such as a lump or nipple discharge, or skin dimpling, probably the five most dangerous words in the English language are "maybe it will go away." A biopsy and histological examination are the only ways of determining with absolute accuracy whether a lesion is benign or malignant, as well as its exact nature, and whether it shows any evidence of precancerous changes. While there are some exceptions in general, a biopsy should be done on patients with any of the following signs or symptoms: (1) all true three-dimensional dominant lumps (even though diagnostic aids are negative, except for cysts which can be safely aspirated under controlled conditions), (2) all suspicious lesions found by x-ray studies of the breast, mammography or xerography (even though there are no clinical findings) and (3) all clear, watery-yellow or serous, pink or serosanguinous, or bloody or sanguinous types of nipple discharge (even though there is no palpable mass, and the cytological examination and the x-ray studies of the breast are negative). Cancer can be present when there are findings such as eczema of the nipple, suspicious axillary nodes or redness of the skin with an underlying induration but when there are not any signs of infection—so-called inflammatory carcinoma. Also included should be any of the following signs that you cannot explain on a benign basis: nipple retraction or elevation, skin dimpling or edema, or a unilateral area of persistent and dominant thickening.

Those are our indications for doing biopsies. I think if we *really* follow this schedule, then we will not be missing or letting patients go on who should have had biopsies.

—HENRY P. LEIS, JR., MD, *New York*

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Refer to: Cram D: Psoriasis—Medical Staff Conference, University of California, San Francisco. West J Med 133: 226-232, Sep 1980

Psoriasis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. NAUGHTON:* *The topic for discussion in this staff conference is psoriasis, and our discussant is Dr. David Cram.*

DR. CRAM:† Psoriasis is a major disease which affects about 2 percent of the population in the United States. Thus, millions of persons are afflicted by this disease, for which there is no cure and for which treatment must often continue for life. Despite intensified and concerted efforts throughout the world, research has yet to uncover the cause of psoriasis. The experimental findings are still in a stage of disarray; however, relevant evidence regarding possible causes is mounting and the pieces of the psoriasis puzzle appear to be falling in place. Dermatologic literature on the treatment of psoriasis has become profuse. Tar and anthralin, old treatments, have come back into vogue; a form of photochemotherapy that combines the use of psoralens and ultraviolet light (called PUVA), has captured the interest of many investigators; and some new treatments such as retinoids and even dialysis have appeared as potential therapies. But as with the pathogenesis of this disease, the treatment of psoriasis can be confusing for practitioners, especially when the potential side effects of each therapy are considered.

I will review some of the clinical characteristics of psoriasis, emphasizing unusual features of the disease, discuss briefly the suspected pathogenic mechanisms and, .inally, present a summary of current methods of therapy.

Figure 1 shows a classic example of psoriasis involving a patient's scalp. The lesions have a sharp margin and often extend onto the forehead. This patient also has psoriasis around ear piercing, an example of the so-called Koebner phenomenon. This phenomenon occurs when a patient with active psoriasis receives an injury to the skin. The disease will develop at the traumatized area within 10 to 14 days. This is just one way the disease can spread.

Nail changes are characteristic. Pitting is said to be a typical feature, although it also occurs in other diseases. Perhaps most characteristic of nail psoriasis is distal onycholysis or distal separation of the nails (Figure 2) with yellowish discoloration. This finding, either on the distal or lateral ends (or both) of the nail plate, is even more diagnostic of psoriasis than is pitting. The hands and feet, palms and soles, can be the major area of involvement in the disease (Figure 3). This

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ABBREVIATIONS USED IN TEXT

PUVA = psoralen-ultraviolet A
AMP = 3′,5′-adenosine monophosphate
GMP = guanosine monophosphate
HLA = human leukocyte antigen

presentation may be confused with a fungal infection or with contact dermatitis. Therefore, it is important to recognize the sharp margination of the lesions and to look for other evidence of the disease, as well as trying to elicit a family history which is usually found in about 30 percent of the cases. The disease can become very extensive (Figure 4), and in an elderly person—particularly one with previous heart problems—varying degrees of high-output cardiac failure can occur. We have seen several patients admitted to hospital with extensive psoriasis and heart failure, in whom clearing of the psoriasis resolved the heart failure to the

Figure 1.—A classic example of psoriasis of scalp.

Figure 2.—Distal onycholysis in psoriasis.

Figure 3.—Psoriasis of the palms and soles.

Figure 4.—Extensive psoriasis involving the entire body.

point that administration of cardiac drugs could be stopped.

Psoriasis may express itself as diffuse tiny or so-called guttate lesions. This variety of the disease sometimes follows a streptococcal infection. It does not carry a different prognosis, but treatment should be started cautiously because in these patients the condition can become worse very rapidly if treated too vigorously at the onset. Psoriasis can take on peculiar configurations at times; serpiginous and linear lesions are often representative of the Koebner phenomenon. Figure 5 illustrates the development of this phenomenon in a woman who cut her legs while shaving. What about surgical wounds in patients with psoriasis? After an operation psoriasis may develop at the site of the incision, but it does not seem to influence healing of the wound.

Psoriasis can be pustular and involve mainly the palms and soles (Figure 6). This variety may be improperly treated for many years due to an incorrect diagnosis. It is important to recognize that the use of systemic corticosteroids in patients with pustular forms of the disease sometimes can precipitate a more generalized and serious pustular form of the disease associated with malaise, fever and other systemic symptoms. This is known as von Zumbusch pustular psoriasis (Figure 7), which can be life-threatening. The most common cause for this development is the use of systemic corticosteroids. In psoriasis, neutrophils are the most common cells in the skin, and with the use of systemic steroids the peripheral neutrophil count increases. This severe pustular form may develop in these patients because many more neutrophils from the circulation have access to the skin. For generalized pustular psoriasis methotrexate is the treatment of choice.

The patient in Figure 8 has an erythema annulare centrifigum form of pustular psoriasis. This could easily be confused with ringworm. This type of pustular psoriasis is not generally severe and will often respond to topical steroid therapy.

Intergluteal pinking can be a clue to the presence of psoriasis when other features may not be so obvious; however, patients may not be aware of its presence. We usually examine this area as well as the scalp and nails to help in the diagnosis of the disease.

An unusual form of psoriasis, called acroder-

Figure 5.—Koebner phenomenon that developed in cuts on the patient's legs.

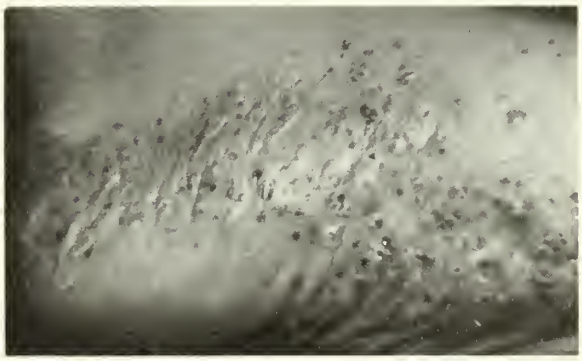

Figure 6.—Pustular psoriasis of the sole.

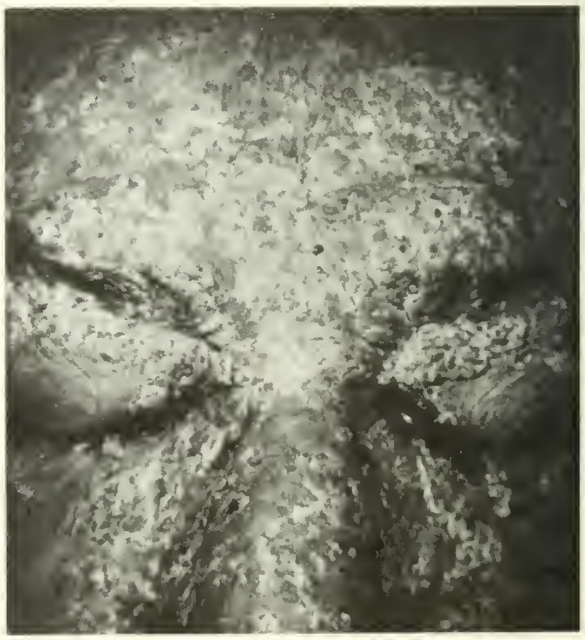

Figure 7.—Acute (von Zumbusch) pustular psoriasis.

matitis continua (see Figure 9), can be easily confused with an infection. This acral form of psoriasis is often very resistant to therapy and, moreover, systemic corticosteroid therapy can lead to the more severe pustular form of the disease.

In rare cases of psoriasis the mucous membranes may be involved. In lingua migrans (Figure 10), for example, a kind of geographical pattern of lesions forms on the tongue. This occurs in some patients with pustular psoriasis, as well as in some patients with Reiter disease.

Psoriatic arthritis typically involves the distal interphalangeal joints, often with associated nail dystrophy (Figure 11) and occasionally with an advanced degree of joint involvement (Figure 12). In 1973 Mole and Wright[1] outlined important aspects of psoriatic arthritis, pointing out that it tends to be asymmetrical, involving a single or only a few small joints in more than 70 percent of the patients. In about 15 percent of patients a symmetrical arthritis occurs which is indistinguishable from rheumatoid arthritis, except that it is seronegative. Arthritis mutalans, often with

Figure 8.—Erythema annulare centrifigum form of psoriasis.

Figure 9.—Acrodermatitis continua form of psoriasis.

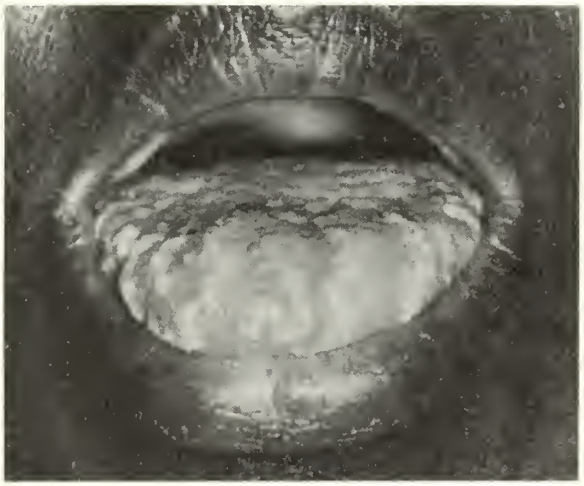

Figure 10.—Lingua migrans is a form of geographic tongue seen in pustular psoriasis.

Figure 11.—Psoriatic arthritis with severe nail involvement.

Figure 12.—A patient with psoriatic arthritis in which there is an advanced degree of joint involvement.

sacroiliac involvement, occurs in about 5 percent of patients with psoriasis. Finally, a strong association of psoriatic arthritis with HLA (human leukocyte antigen)-B27 has been observed.

The histologic features of dermal psoriasis are characteristic, including lamellar hyperkeratosis with parakeratosis, pronounced acanthosis and often a number of mitotic figures in the epidermis. There are dilated blood vessels in the upper dermis and neutrophils are present. These changes result from abnormal keratinization. Formation of keratin does not occur at a normal rate in persons with psoriasis; instead, the rate of turnover of epidermal cells is much more rapid than usual. This leads us to consider the pathogenesis of psoriasis, the first aspect of which is the genetics of the disease.

Pathogenesis of Psoriasis

At present, psoriasis is thought to be primarily an autosomal dominant disease with environmental factors playing a role. It is therefore called a multifactorial disease. One important association is with the human leukocyte antigen (HLA) markers. An increased number of several specific B alleles, including B13, B17, Bw16 and Bw37, have been found in patients with psoriasis. A significant increase in HLA-B27 antigen levels has been detected in patients who have psoriatic arthritis or pustular psoriasis. More recently, some of the newer HLA antigens have been described; it now has been found that the association of HLA-Cw6 and HLA-Dw11 with psoriasis is greater than that of the specific B antigens.[3] However, we do not yet understand the significance of these HLA findings. All we can say is that the presence of these specific lymphocytic antigens indicates that either the patient has psoriasis or has a propensity towards the development of the disease.

Factors that are thought to be involved in development of psoriasis are abnormalities of cyclic AMP (3′,5′-adenosine monophosphate), the prostaglandins and, more recently, the polyamines. Cyclic AMP and cyclic GMP are the so-called intracellular second messengers for hormones and neurotransmitters acting on the cell surface. They regulate epidermal cell growth and have been studied extensively in psoriatic epidermis. It was originally proposed that a major cause of psoriasis was a decrease in cyclic AMP levels in psoriatic skin. However, further experimental findings have indicated that cyclic AMP levels may appear to be either elevated or normal depending on the experimental technique used.[4] Cyclic GMP is elevated in psoriatic lesions, but more studies are needed before we will have a clear understanding of the role of the cyclic nucleotides in psoriasis.

In psoriatic lesions prostaglandins levels are elevated as well. These are hormone-like substances which are formed from arachidonate and released from the cell membranes by a phospholipase. They are degraded locally in the skin and do not circulate. Their functions include raising the intracellular levels of cyclic AMP, dilating cutaneous vessels and participating in inflammatory reactions, of which psoriasis is an example. In psoriatic skin there is an elevation of the arachidonate and leukocytotactic factor. This factor may be in part responsible for the chemotaxis of neutrophils to the psoriatic lesion.

The newest substances studied are the intracellular polyamines, putrescine, spermidine and spermine, which are involved in the regulation of cellular proliferation. In rapidly proliferating tissues the formation of these amines occurs just before and during the early part of DNA synthesis. It has been shown that even in the uninvolved epidermis of patients with psoriasis (as compared with persons without psoriasis) there are increased levels of polyamines. There are also increased polyamine levels in the urine and in the blood of patients with psoriasis.[5] When the polyamine levels are elevated, cell proliferation tends to be accelerated. Thus, polyamines may have some influence on the enhanced cellular proliferation that occurs in psoriasis, or they may be elevated as a secondary phenomenon.

Recently, in psoriatic skin there has been de-

TABLE 1.—*Major Forms of Therapy for Psoriasis*

Tars
Ultraviolet light
Anthralin
Corticosteroids
Retinoids
Antimetabolites
Dialysis
Photochemotherapy (psoralens and ultraviolet light)

TABLE 2.—*Indications for Methotrexate*

Psoriatic erythroderma
Psoriatic arthritis
Acute pustular psoriasis—von Zumbusch type
Localized pustular psoriasis
Extensive psoriasis that is recalcitrant to other therapies

tected a protease which also acts as a leukocytotactic factor. The enzyme is known to activate the fifth component of complement. In addition there appears to be altered monocyte function in psoriasis. For example, the monocytes seem to have unusual phagocytic properties. The peripheral leukocytes may also be sticky and have increased physiological activity, the significance of which is not yet known.

Immunologic events in psoriasis until recently have not been considered important. The finding of the deposition of IgG in the stratum corneum is thought to be one possible mechanism for the production of the disease. The problem with this suggestion is that similar immunoglobulin deposits have been found in the skin of patients without psoriasis as well as in some patients with other hyperproliferative diseases. Some patients with psoriasis, particularly those with arthritis, have been found to have circulating immune complexes as well as increased levels of IgG antiglobulins. Cell-mediated immunity may also be disturbed because patients with psoriasis can have a decreased number of circulating T cells.[6] The significance of all of these recent findings awaits further investigation.

Treatment

The major forms of therapy for psoriasis are listed in Table 1. The oldest is the use of topical tars and ultraviolet light, the so-called Goeckerman regimen which was first reported successful in 1925. It remains as a therapy which has withstood the test of time as being uniformly safe and effective in the treatment of psoriasis.[7] There has not been an increased incidence of cutaneous carcinoma in patients treated by the Goeckerman regimen, even though these are two carcinogenic agents; the reason for this fact is not clear. It appears that patients with psoriasis have a decreased propensity for the development of cutaneous carcinoma. Tar and ultraviolet light when combined in the treatment of psoriasis appear to reduce DNA synthesis in involved skin. When carried out for two to four weeks, such combined therapy results in a clearing of the disease and long remissions. Side effects are minor and infrequent.

Anthralin, which is popular in Europe and in a few centers in the United States, is structurally similar to acridine, and acts by inhibiting DNA synthesis, thereby reducing the rapid epidermal cell turnover rate. Anthralin, however, tends to stain and is a primary irritant except in low concentrations. When used in the so-called Ingram technique, anthralin can produce clearing of psoriasis in about 20 days, but the remissions tend to be shorter than those due to tar. Topical corticosteroids are elegant, easy to apply, cosmetically acceptable and are used commonly in the treatment of psoriasis. However, they are associated with tachyphylaxis (defined as the rapid onset of tolerance to an action of a drug administered over a short time). This is one major drawback to the use of topical steroids in psoriasis; the other is that if used extensively (particularly the more potent topical steroids) they can precipitate pustular psoriasis. A suppression of the pituitary adrenal axis has been reported in patients using the newer, more powerful topical corticosteroids over large areas of the body.[8] A pharmacological dilemma exists in trying to produce a topical corticosteroid that is potent enough, but that will also remain locally in the area applied, thereby producing the therapeutic effect desired. Local skin changes of atrophy, purpura and acneform eruptions also may occur, which can make the continuous use of topical steroids in psoriasis difficult.

Of the systemic therapies for psoriasis, methotrexate appears to be the best. The indications for its use are listed in Table 2. I always try to obtain a liver biopsy specimen from all my patients before using methotrexate because the use of this drug over a long time can lead to cirrhosis[9] I also repeat the liver biopsies every two years while the patient is receiving the drug. In addition, leukocyte and platelet counts are taken every two weeks during initial therapy and then at least once monthly. Effective dosages of methotrexate are an initial dose of perhaps 25 mg, given either

intramuscularly or orally in a single dose and followed by 15 mg once a week thereafter. Few patients obtain 100 percent remission with these dosages, but significant clearing of the disease occurs in 75 percent of them.

Recently, peritoneal and hemodialysis have been found effective in clearing psoriasis in some patients. However, controlled studies with double-blind comparisons have not been completed. Peritoneal dialysis seems to work best but it should be tried only in chronic, severe, disabling cases that have proved resistant to conventional therapy and to methotrexate.[10] With peritoneal dialysis, pain and inconvenience occur in 100 percent of patients and peritonitis is a significant side effect. One can only speculate as to the therapeutic basis of this modality in psoriasis if it ever proves to be a worthwhile and reasonably safe procedure in severe, recalcitrant psoriatic cases.

The retinoids are derivatives of vitamin A and have an effect on formation of keratin. Their use for the treatment of psoriasis is still in the experimental stage in the United States. As a form of therapy they seem to provide a rapid initial response but low maintenance doses do not appear effective. Complete clearing of psoriasis occurs in about 60 percent of patients and side effects are frequent.[11] They include cheilitis, rhinitis, pruritus, dryness and fragility of the skin, and diffuse hair loss. The retinoids remain as investigative drugs at present, and their role in treating psoriasis may prove to be primarily that of synergistic adjunct with other topical therapies being used.

One of the most extensively studied newer treatments is use of PUVA, that is, psoralen-ultraviolet A.[12] There are three forms of ultraviolet light: UVC, which are the very short rays that do not reach the earth's surface because they are filtered out by the ozone layer, UVB, or sunburn rays and UVA which are the longer ultraviolet rays, which can pass through window glass. The psoralens come from a plant in Egypt and the form used in psoriasis is 8-methoxypsoralen. When taken in combination in psoriasis, UVA and psoralens not only produce tanning of the skin, but also a clearing of the psoriatic lesions. The mechanism involves the formation of light-induced DNA crosslinks which inhibit DNA synthesis. It is a convenient outpatient treatment. The patient simply takes the psoralen tablets two hours before therapy two days a week and then receives a dose of ultraviolet light in increasing amounts twice a week for 20 to 24 treatments. The skin will clear in 85 percent of patients treated. Unfortunately, the skin does not stay clear without maintenance therapy of from once every two weeks to once a month. The major disadvantage of this treatment is the short remission times; it seldom produces long-range clearing of the skin without relapses. Other significant problems are the production of aging of the skin and skin cancer with this modality. An increased incidence of skin cancers has been reported following PUVA therapy in patients with very fair skin, those who have had previous x-ray therapy for their psoriasis, and those who have had skin cancer previously.[13] The eyes must be carefully protected by appropriate glasses during therapy and for at least 24 hours after therapy because the lens of the eye is an ectodermal structure which also absorbs the psoralen. PUVA has not yet been approved for general use by the Food and Drug Administration and awaits further experimental study.

Conclusion

At present, we have no ideal treatment for psoriasis; that is, one which is simple and easily administered, leads to rapid and complete clearing of the disease, suppresses recurrences and is systemic in type, does not affect the patient's well being or activities and is without significant side effects. However, with proper selection of available treatments, we are able to clear or lessen the severity of psoriasis in a substantial number of patients, and the future holds promise of better things to come.

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Important Advances in Clinical Medicine

Epitomes of Progress — Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in internal medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Digoxin, Quinidine and Sudden Death

THE INTRODUCTION OF QUINIDINE into clinical practice in 1918 marked the beginning of effective therapy for cardiac arrhythmias. The use of quinidine to convert atrial filbrillation to sinus rhythm, however, was associated with a high incidence of sudden death (estimated at between 2 percent and 4 percent). This phenomenon of quinidine syncope occurred almost entirely in patients who were also receiving digitalis. An explanation for this phenomenon has recently been discovered: Addition of quinidine to digoxin therapy causes a dramatic increase in levels of digoxin in the blood.

Levels of the drug in the body are initially determined by body size (volume of distribution) and at steady state by elimination processes (clearance). In a typical patient taking digoxin, about 50 percent of the daily dose is excreted in the urine; the reminder is cleared by metabolic and fecal loss. Quinidine decreases the volume of distribution of digoxin by displacing it from tissue binding sites. This leads to a rapid rise in digoxin concentration and an increase in cardiac effect. Quinidine also quickly decreases the elimination of digoxin by both renal and nonrenal routes, leading to a twofold increase in the drug's concentration over a week's time. The combined effects of decreased tissue binding and impaired clearance cause an immediate and sustained elevation of digoxin levels in the body.

Cardiac toxicity may be a consequence of this raised level alone; however, this condition is made more severe by quinidine-induced prolongation of ventricular repolarization (shown by prolonged QT interval), leading to ventricular tachyarrhythmias, syncope and sudden death.

The pharmacokinetic interaction also occurs between digitoxin and quinidine, but not with procainamide or disopyramide. Patients with renal impairment may be particularly at risk because they rely almost entirely on nonrenal elimination of digoxin, which is virtually abolished by the action of quinidine. It would seem prudent to stop digoxin therapy for two days after starting quini-

dine, and then to resume administration at half the original dose if digoxin levels are to remain the same. The serum concentration should be checked after the patient has been on the new regimen for a week.

Quinidine-digoxin toxicity should be treated by discontinuing administration of both drugs. The rapid elimination of quinidine will lead to a fall in digoxin concentration as the volume of distribution of digoxin increases. Lidocaine, bretylium and overdrive-pacing have proved effective in treating arrhythmias, but drugs which prolong the QT interval, such as procainamide and disopyramide should be avoided.

NICHOLAS H. G. HOLFORD, MSc, MRCP(UK)

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Prescribing Exercise

INDICATIONS FOR RESTRICTING ACTIVITY until recently have been more clearly defined than indications for exercise. From data accumulated over the past 20 years, guidelines for prescribing exercise have been developed.

A patient's history, findings on physical examination and a multistage exercise test (MSET) form the basis from which an exercise prescription is determined. From the MSET the target heart rate for exercise (peak heart rate and the maximum work load) is derived and the patient can be advised of other activities of equivalent workload which he or she can safely carry out.

The exercise prescription should specify the frequency, intensity, duration and type of exercise. A minimum of three days of exercise a week, preferably nonconsecutive days, is necessary. High-intensity exercise is neither enjoyable nor safe for cardiac patients. Each patient should be advised to exercise to maintain a heart rate of 70 percent to 85 percent that achieved on the MSET. The exercise most easily undertaken, most readily monitored and most often prescribed is walking. Other endurance activities such as jogging, cycling and swimming can also be prescribed.

The usual exercise session should last about an hour, with 10 minutes of warm-up, 20 to 50 minutes of endurance exercise and 5 to 10 minutes of cool-down. The warm-up and cool-down periods are important and should not be omitted because they serve to develop and maintain flexibility and muscle strength as well as reducing the risk of muscle problems, injuries and fatigue.

A patient's initial level of fitness and clinical status are important considerations when developing the exercise prescription. Typically, an asymptomatic patient who seeks advice concerning exercise is over 40 years old, has a major coronary risk factor or suspected coronary artery disease and has been inactive for some years. Therefore, initial exercise sessions should be short and more frequent. Patients with established cardiac disease or a chronic illness will also need a slow initiation into exercise and special attention to medications that may affect such exertion. Early low-level treadmill testing and exercise for patients after myocardial infarction and myocardial revascularization operations are safe and advantageous. Periodic review and repeat MSE testing are required to adjust the target heart rate with exercise.

Exercise is a lifelong commitment and is most valuable when it is a component of a treatment program that deals with all the cardiovascular risk factors that can be modified or controlled.

PATRICK M. MOLONEY, MB, MRCPI

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Intracavitary Electrodes for Diagnosis and Treatment of Arrhythmias

ALTHOUGH SEVERAL ARTICLES have reported the use of right atrial intracavitary electrode electrogram monitoring and therapeutic pacing for diagnosis and treatment of atrial arrhythmias, this modality unfortunately has had limited use.

It is well recognized that an arrhythmia such as atrial flutter with 2:1 atrial ventricular conduction may be extremely difficult to diagnose. This form of atrial flutter may be confused with sinus, atrial or junctional tachycardia. If aberrant ventricular conduction is present, confusion with ven-

tricular tachycardia is likely. An intracavitary right atrial electrocardiogram can be helpful in differentiating these arrhythmias.

The use of an intra-atrial electrogram provides magnification of the atrial electrical activity. If an atrial electrocardiogram (ECG) is compared with simultaneous surface leads using any standard three-channel ECG machine, diagnosis of the arrhythmia is greatly facilitated.

Once the diagnosis is established, the same intracavitary electrode can be used for rapid atrial pacing with an external pacemaker unit designed to pace up to rates of 800 beats per minute. Virtually all forms of tachyarrhythmia with the exception of sinus tachycardia, type II atrial flutter, atrial fibrillation and ventricular fibrillation may respond to rapid atrial pacing with conversion either to sinus rhythm or to a less threatening arrhythmia that is amenable to combined medical treatment. If type I atrial flutter with rapid ventricular response rate recurs despite interruption with right atrial rapid pacing, a more desirable atrial tachyarrhythmia may be induced by pacing the atria at a rate of 450 to 500 beats per minute to produce atrial fibrillation. The ventricular response rate may then be controlled by adding digitalis to the treatment regimen.

In a recent review the use of cardiac electrodes in the diagnosis and treatment of tachyarrhythmias was summarized. The use of rapid atrial pacing has few adverse side effects and is desirable in acutely ill patients who present a high anesthetic risk for external electrical cardioversion.

DALE M. ISAEFF, MD

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Vasodilator Therapy for Chronic Congestive Heart Failure

STANDARD MEDICAL THERAPY for chronic congestive heart failure includes reduction of cardiac workload, restriction of salt, and administration of diuretics and digitalis. In patients who do not respond well to this regimen, admission to hospital may be required to control symptoms and signs of heart failure. Over the past several years, vasodilator drugs, which are given in addition to digitalis and diuretic therapy, have become available. Results suggest that many patients will benefit from the addition of these drugs and will be symptomatically improved.

Vasodilator drugs can be divided into several subgroups, depending on their mechanism of action. Arteriolar dilators, such as hydralazine, reduce systemic vascular resistance, making it easier for the heart to pump blood throughout the body. This increase in cardiac output is usually accompanied by little or no change in heart rate, mean arterial pressure, or left and right atrial pressures. Vasodilators that predominantly dilate peripheral veins, such as the nitrates, work by a different mechanism. Because 75 percent of the blood volume is located in the peripheral venous system, dilation of veins will tend to increase the relative amount of blood in the peripheral veins and reduce the volume of blood in the chest. This is helpful in lowering left and right atrial pressures, thereby relieving the signs of pulmonary or systemic congestion.

The nitrates can be administered effectively by the sublingual, oral or topical route. Because of their shorter course of action when given sublingually, these drugs are usually administered orally or topically to patients with chronic congestive heart failure.

A combination of arteriolar and venodilating drugs, which can reduce right and left atrial pressures and increase forward cardiac output, have been extremely beneficial in many patients with severe chronic congestive heart failure. A single drug that has combined arteriolar and venodilating effects is prazosin hydrochloride. Some studies have shown hemodynamic tachyphylaxis with prazosin therapy, wherein the magnitude of the hemodynamic response diminishes with successive doses. Nevertheless double-blind placebo-controlled exercise studies have shown improved exercise tolerance in patients receiving this postsynaptic alpha-adrenergic blocking agent. Several other new drugs are being tested to evaluate their potential as therapeutic agents in chronic congestive heart failure, and it is likely that a variety of drugs may be available in the future.

In patients admitted to hospital for chronic refractory heart failure, it is helpful to pass a bal-

loon-tip Swan-Ganz catheter for measurement of hemodynamics. The immediate response to vasodilators can then be titrated to achieve an optimal dosage schedule before a patient is discharged from hospital. In patients with mitral regurgitation, both arteriolar and venodilators have been particularly beneficial. The administration of these drugs decreases the regurgitant fraction and left atrial pressure while increasing forward cardiac output. Because many patients with chronic congestive heart failure have some degree of mitral regurgitation, vasodilators are a particularly attractive form of adjunctive therapy in this subgroup.

In summary, vasodilator drugs provide an important form of adjunct therapy in patients with severe, chronic congestive heart failure. Available drugs are effective, and new drugs are being evaluated. Results to date suggest that this form of therapy has a permanent place in the pharmacological management of heart failure.

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Resurgence of Plague

In recent years there has been an increasing incidence of plague reported from endemic areas of the western United States. This is due in part to natural fluctuations of the plague reservoir involving the organism *(Yersinia pestis),* its vector (fleas) and hosts—small mammals indigenous to the region. However, a more important reason for this increase is greater contact between humans and animals carrying the disease. Many cases occur on Indian reservations where the life-styles of the Native Americans bring them into closer contact with the sources of infection. However, increased popularity of rural life-styles as well as backpacking and camping activities has increased the incidence of plague in other than Native Americans. Therefore, physicians practicing in urban and nonendemic areas also need to be aware of the possibility of the disease occurring in patients who have visited endemic areas.

The disease has an incubation period of two to six days, followed by initial manifestations such as malaise, fever, and pain and swelling in the area of regional lymph nodes (usually inguinal or axillary). Progression of the disease is variable; however, in most untreated patients septicemia develops. Pneumonic forms are unusual but do occur.

Diagnostic efforts should be expeditious, including aspiration of lymph nodes (buboes), cultures of blood and sputum, and examination of cerebrospinal fluid. Aspirated material should be stained with Wayson or Giemsa stains to delineate the bipolarity of the organism. A fluorescent antibody method is available for rapid presumptive diagnosis. Serologic testing can be done for later confirmation.

Streptomycin is the antimicrobial drug of choice. Tetracycline and chloramphenicol are good alternative drugs. Studies are underway to determine the efficacy of other aminoglycosides. Usual supportive measures should be used for controlling endotoxic shock that may complicate septicemia due to plague. The patient should be isolated and his or her contacts found and treated with antimicrobial prophylaxis where appropriate.

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Pneumococcal Polysaccharide Vaccine

With the advent of effective antibiotic therapy in the late 1940's, there has been less concern with pneumococcal infections. However, the problem has not disappeared and, in spite of the effectiveness of treatment, more than 400,000 cases of pneumococcal pneumonia occur annually in the United States, with a mortality of between 5 percent and 10 percent. This means that as many as 40,000 people a year die from pneumococcal pneumonia. It is also estimated that there are between 3,000 and 5,000 cases of pneumococcal meningitis each year, and that approximately 6 percent of these cases are fatal. At least 83 types of pneumococci are responsible for the infections,

and these strains can be identified by their capsular polysaccharides. Patients at high risk for pneumonococcal infections are those with sickle-cell anemia, those in whom the spleen is absent or malfunctioning, and those with agammaglobulinemia, multiple myeloma, nephrotic syndrome, cirrhosis or alcoholism.

Attempts to develop pneumococcal vaccines began more than 50 years ago. A trivalent vaccine tested during World War II was found to be effective. Another vaccine which contained several polysaccharide types was licensed and produced in the United States in the mid-1940's. However, when antibiotics became available, its production was discontinued.

Recently, a polyvalent vaccine that contains 14 of the most prevalent capsular types has become available in the United States. These 14 types account for 80 percent or more of the incidence of pneumococcal disease occurring in this country. The vaccine has been widely tested in susceptible groups and has been found to be more than 80 percent effective.

The Public Health Service Advisory Committee on Immunization Practices of the Center for Disease Control has issued the following guidelines for the use of the pneumococcal vaccine:

- Mass immunization is not recommended at present.
- Use in treating pregnant women or children under two years of age is not advised.
- The vaccine is of greatest value to the following: Anyone over two years of age lacking a spleen, anatomically or functionally, such as those with sickle-cell disease, and persons over two years of age in whom risk of pneumococcal disease is higher because of chronic illnesses such as diabetes mellitus, functional impairment of cardiorespiratory, hepatic or renal systems or lack of immune responsiveness. Because the risk of development of or death from pneumococcal disease increases with age, the benefits of receiving the vaccine also increase with advancing age.

A single dose of 0.5 ml of vaccine is given subcutaneously or intramuscularly. The vaccine should not be injected intravenously. Also, booster injections should not be given more than once every three years. The only adverse reactions are local erythema and soreness at the injection site, which usually last less than two days. A low-grade fever with temperatures of less than 38.3°C (101°F) may occur during the first 24 hours.

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New Conceptual and Technical Advances in the Care of Diabetes

RECENT CONCEPTUAL AND TECHNICAL ADVANCES in the management of diabetes mellitus should have a major impact on delivery of health care. These advances include (1) more stringent but rational diagnostic criteria, (2) improved assessment of metabolic control and (3) new technology in the administration of insulin.

Over the past two decades, several large studies have shown that diabetes-associated complications occur in specific subgroups of glucose-intolerant persons. New criteria more accurately restrict the diagnosis of diabetes to those who are at increased risk for the development of specific complications such as ketosis, retinopathy and nephropathy. Normal levels of glucose in venous plasma should be less than 115 mg per dl, and two hours after oral administration of glucose they should be less than 140 mg per dl. To be considered diabetic a person must have (1) classic symptoms of diabetes such as polyuria, ketonuria and unequivocally elevated levels of circulating glucose, (2) fasting venous plasma levels of glucose that exceed 140 mg per dl on more than one occasion or (3) one or two hours after glucose ingestion, venous plasma levels of glucose that exceed 200 mg per dl on more than one occasion.

These criteria define a subgroup of persons who have (1) a glucose intolerance in the normal to diabetic range, (2) a risk of 1 percent to 5 percent per year for the development of diabetes and its complications and (3) a high potential for normal glucose tolerance in the future. New criteria have also been suggested for children and pregnant women. After the diagnosis of diabetes is established, it is suggested that further subgroups be identified, primarily to determine whether a patient requires insulin (insulin-dependent dia-

betes) or some other treatment regimen (noninsulin-dependent diabetes). Although these concepts are not new, this terminology focuses attention toward a treatment regimen independent of age or habitus. Because of the ambiguities of the terms juvenile onset and maturity onset, it is suggested that they no longer be used. Much of the confusion involving the pathogenesis, complications and treatment of diabetes results from inadequate information concerning the diagnosis, as well as mixing of patients with dissimilar types of diabetes.

Routine clinical assessment of the metabolic abnormalities associated with diabetes is less than ideal. Insulin is a major regulator for physiological processing and storage of nutrients. During states of insulin bioinactivity, regardless of whether the cause is islet secretory impairment or peripheral insulin resistance, major alterations occur in lipid, protein and carbohydrate homeostasis. For the past several decades, metabolic control has been evaluated by sharp changes in glucose levels in urine or blood. Routine estimates of lipid and protein levels are virtually nonexistent. Recent technical advances in the specific estimation of erythrocyte hemoglobin A1C, a naturally-occurring glycosylated hemoglobin species, have provided for a longer-range assessment (one to three months) of metabolic control. Specific hemoglobin A1C assays correlate with circulating glucose concentrations, are available for routine clinical use and, when inappropriately elevated, provide a marker indicating the necessity for more stringent metabolic control. Although hemoglobin A1C levels offer an improvement for assessing metabolic control with regard to both health care delivery and research, the assay apparently remains restricted to glucose homeostasis.

Recent technology applied to improving metabolic control of insulin-dependent diabetes has proved effective in research, and has limited but immediate health care uses. One of these bioengineering products incorporates a blood glucose sensor and computer analysis to direct the intravenous infusion of insulin. This glucose-controlled, artificial pancreas reliably restores circulating glucose levels to normal, and other metabolic measurements to near normal, irrespective of meal patterns. This devise is also useful for complex surgical, medical or obstetric care of patients with diabetes. These units will become more generally available over the next few years; at present, the San Francisco and Irvine campuses of the University of California are using them for health care delivery and research. For outpatient care of persons with insulin-dependent diabetes, portable, nonglucose-controlled, variable rate, subcutaneous infusion pumps are available. These instruments are also in active use for research and patient care. The portable insulin pump has been shown to improve circulating glucose, lipid and amino acid levels. Associated with improved metabolic control resulting from use of these two devices, is improvement in control of urinary albumin leakage and improved nerve conduction velocities after only three weeks and 48 hours, respectively. Several caveats remain unexplored such as the psychosocial impact of such devices on patients, but these and other issues are being investigated.

New conceptual and technical advances in the understanding and management of diabetes has had a major impact on health care delivery and research. It is hoped that such changes will improve the course of patients with chronic diabetic complications.

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Endoscopic Sphincterotomy in the Therapy of Extrahepatic Cholestasis

SINCE 1970, endoscopic retrograde cholangiopancreatography (ERCP) has become an established diagnostic technique in the management of pancreatic and biliary tract disease. The ability to direct instruments through the duodenoscope into the biliary ducts subsequently influenced the development of endoscopic sphincterotomy (ES), a sophisticated electrosurgical technique for the removal of common duct stones (CDS). Widely used first in Japan and Europe, and later in the United States, endoscopic sphincterotomy is now an established, clinically accepted therapy for removal of retained or recurrent CDS after cholecystectomy. Other situations in which it may be

of value are CDS in some high-risk patients or those with pepticemia and intact gallbladders (ES may be either a substitute or preparation for a later operation); short distal common bile duct strictures, and functional obstruction of the distal bile duct, often called papillary stenosis (PS). Papillary stenosis remains an ambiguous clinical entity and requires further study to confirm the role of ES in its management. Endoscopic sphincterotomy should be avoided when patients have a severe coagulopathy, a long stricture of the common duct or stones larger than 2.5 cm.

The technique most commonly used has been presented in detail in the literature but it continues to be studied and improved. A catheter designed for electrosurgical use is passed through the duodenoscope into the distal biliary tree where a short incision is created. CDS may be extracted with a balloon-tipped catheter, Dormia basket or allowed to pass spontaneously. The incision often remains as a permanent choledochoduodenostomy.

The results of endoscopic sphincterotomy as carried out by experienced European and American endoscopists have been similarly successful. ES permits extraction of stones or their spontaneous passage in 88 percent to 92 percent of patients receiving this therapy. Relief of symptoms following ES in carefully selected patients with PS has yielded promising results. This author's (F.C.S.) series includes 38 successful CDS extractions in the 41 patients undergoing the procedure and 2 patients who have been successfully relieved of symptoms secondary to papillary stenosis.

Reported complications include bleeding, retroperitoneal perforation, pancreatitis and cholangitis occurring cumulatively in 8 percent to 10 percent of cases. Subsequent operations have been required in 2 percent to 3 percent of these, with an overall mortality of 1 percent to 1.5 percent. The present series includes two patients who had minor bleeding and one patient in whom both pancreatitis and perforation required an operation, for an overall complication rate of 8 percent. No deaths occurred among the 43 patients in whom ES was carried out.

The long-term outcome of ES appears to be comparable to that obtained by laparotomy. By contrast, morbidity, mortality and cost, especially when considering the number of hospital days involved and cost of ancillary procedures, are substantially lower than those required for laparotomy, As with ERCP, the skill required to master ES demands extensive experience and competent training. Potential complications of the procedure require immediate availability of and a good working relationship with an experienced biliary tract surgeon. Therefore, the procedure should be made available only in those centers where there are physicians with established expertise who can be assured of cooperative support.

Although it carries known mortality and morbidity risks and demands sophisticated expertise, ES is an established, cost-effective clinical technique now available in many regional centers throughout the United States.

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Granulocyte Transfusion: Its Current Status

ERYTHROCYTE, PLATELET AND PLASMA components of whole blood have been available for prophylactic and therapeutic treatment for many years. However, the recent availability of sophisticated and economic equipment for safe extracorporeal blood cell separation has enabled many blood banks to offer clinicians fresh whole blood preparations enriched with leukocytes (so-called leukocyte or granulocyte transfusions). Two procurement methods are used at present: filtration leukapheresis (FL), and continuous flow or intermittent flow centrifugation leukapheresis (CFC, IFC). Of these two methods, the CFC and IFC products are associated with fewer side effects for donors and recipients, and contain better functioning granulocytes. Because of these reasons the FL procedure has been abandoned by the National Red Cross and probably will not be widely used in the future by others.

Leukocyte transfusions are of greatest value in the treatment of patients with neutropenia secondary to diminished neutrophil production. They can be used prophylactically to prevent bacterial infections or therapeutically to treat established

bacterial infections. Prospective, randomized clinical trials of both prophylactic and therapeutic transfusions have been recently completed. It has been found that HLA matched prophylactic granulocyte transfusions decrease the incidence of bacterial infection developing in patients with neutropenia who are receiving bone marrow transplants; however, it has not been found to be any better than laminar air flow isolation. In non-HLA matched transfusions, however, the incidence of alloimmunization against leukocyte antigens severely limits its prophylactic use. In several therapeutic trials involving neutropenic patients with acute leukemia and aplastic anemia, transfused patients appeared to fare better than nontransfused patients; although, in some studies the differences were not statistically significant. This is due to variability in the types and amounts of granulocytes transfused in the different studies. Transfusions were of no benefit in patients with "fevers of undetermined origin" or in patients with neutrophil counts of over 1,000 per μl. The efficacy of granulocyte transfusion was directly related to the ability of the product to raise the granulocyte count in the recipient, so that smaller patients, or those given large daily or twice daily transfusions were more likely to benefit. In considering this form of therapy, two points should be noted. First, although some patients' conditions clearly improve with therapy, no studies have shown a definite increase in survival rates for patients receiving granulocyte transfusion. Second, no benefit is achieved in recipients for whom results of bone marrow examinations would predict recovery of neutropenia within three to five days. Granulocyte transfusions probably are most effective in causing improvement or cure of clinical infection when used in the following circumstances: (1) The patient has documented serious bacterial infection that remains unresponsive after 24 to 48 hours of parenteral broad spectrum antibiotic treatment, (2) the patient's neutrophil count is less than 500 per μl, with absent neutrophil precursors in the marrow, (3) healthy compatible donors, equipment and personnel for long-term support are available and (4) the patient has a good prognosis if recovery from the infection is obtained.

In spite of good evidence that granulocyte transfusions can alter the clinical course of serious bacterial infections in some patients with neutropenia, the modest overall benefit and inconvenience of daily procurement dictate that this therapy in general clinical practice should be reserved for selected patients.

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Progress Toward Effective Antiviral Agents

WHILE MANY VIRAL INFECTIONS are associated with illness and loss of work, serious consequences from such infections are unusual. However, aggressive treatment of diseases such as neoplasia or renal failure often involves therapies that alter the immune system and predispose patients to more serious viral infections. Thus, progressive viral diseases in immunosuppressed patients and occasional severe infections in otherwise healthy persons have served as incentives to the development of effective antiviral compounds. Recent events have suggested that such therapy exists. Three distinct substances have proved effective against viral infections when used in other than topical applications.

Amantadine is known to be an effective prophylactic agent when used to prevent infections with influenza A. This drug appears particularly useful in patients with serious underlying diseases who are exposed to outbreaks of influenza caused by this strain before immunization can be expected to produce reasonable antibody titer. Amantadine also appears of therapeutic value after the first symptoms of influenza have developed. However, its usefulness in this regard may be limited, and no information is available to suggest whether it is effective against influenzal pneumonia, the most hazardous complication.

Adenine arabinoside, a relatively new agent, has proved of definite benefit in patients with encephalitis due to herpes simplex virus, and has been effective in reducing mortality. In addition, adenine arabinoside may be effective in herpes zoster

and disseminated herpes infections in newborn infants.

Interferon, a natural body protein, has been produced in vitro in quantities sufficient for administration to patients and has been found effective against herpes zoster. However, it remains both difficult and expensive to produce.

In addition to the parenteral drugs mentioned, idoxuridine has long been an effective topical therapy for treatment of certain forms of herpetic keratitis, and topical adenine arabinoside appears even more beneficial in ocular disease.

Newer agents with considerable promise are being tested. They include acycloguanosine (Acyclovir), which is much more effective in vitro than adenine arabinoside against herpes viruses, and the glucose derivative 2-deoxy-D-glucose, which has been reported to be beneficial for genital herpes infections when applied topically.

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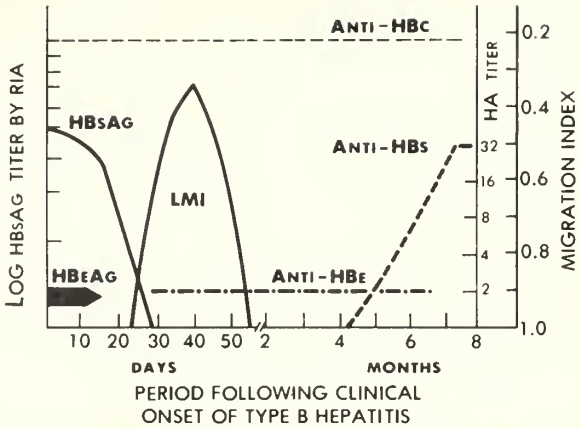
Immunodiagnosis of Viral Hepatitis

LABORATORY DIAGNOSIS OF HEPATITIS types A, B and non-A/non-B (abbreviated HA, HB and NANB, respectively) can be established by testing immunologic responses to the viral agents of HA and HB; NANB is established only by exclusion (Table 1).

In HA, the presence of anti-HA in the IgM class of immunoglobulins suggests a current or recent infection, whereas anti-HA appearing in the IgG class indicates infection occurring in the past and confers immunity to HA.



Anti-HBc = hepatitis B core antibody; Anti-HBe = hepatitis B "e" antibody; Anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B "e" antigen; HBsAg = hepatitis B surface antigen; RIA = radioimmunoassay.

Figure 1.—Immunologic response to HBsAg, HBcAg and HBeAg during acute and convalescent phases of type B hepatitis. The fact that leukocyte migration inhibition (LMI) with purified HBsAg is present but disappears after about four weeks suggests that hepatitis B virus infection may be self-limited. In contrast, the LMI test is negative in persistent or chronic cases of hepatitis B.

The temporal changes in various markers during the acute phase of HB are shown in Figure 1. Although the clinical manifestations of acute HA, HB or NANB are similar, a chronic carrier state and chronic liver disease of more than six months duration are recognized only for infection with HB or NANB agents. Nearly 10 percent of patients with acute HB have unresolved hepatitis, frequently persisting for years, and often progressing to a

TABLE 1.—*Practical Guide for the Interpretation of Serologic Markers of Viral Hepatitis*

Clinical Interpretation	*IgM Anti-HA**	*HBsAg*	*HBeAg*	*Anti-HBe*	*Anti-HBc*	*Anti-HBs*
Acute HA	+	−	−	−	−	−
Incubation period or early acute HB	−	+	+	−	−	−
Acute HB	−	+	+	−	+	−
Fulminant HB	−	+	−	−	+	+/−
Convalescence from acute HB	−	−	−	+	+	+/−
Chronic HB	−	+	+/−	+/−	+	+/−
Persistent HB carrier state	−	+	−	+	+	−
Past infection with HB virus	−	−	−	−	+	+
Infection with HB virus without detectable (excess) HBsAg	−	−	−	−	+	−
Immunization without infection	−	−	−	−	−	+
Non-A/non-B hepatitis by exclusion of markers for HA and HB	−	−	−	−	−	−

Anti-HA = hepatitis A antibody; HBsAg = hepatitis B surface antigen; HBeAG = hepatitis B "e" antigen; anti-HBe = hepatits B "e" antibody; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody.

*Clinically unrecognized infection occurring in childhood accounts for the high incidence of IgG anti-HA antibodies in 80 percent to 90 percent of adults in underdeveloped countries as compared with 25 percent to 50 percent of adults in Europe and the United States.

form of chronic hepatitis. The pathogenic mechanisms responsible for the persistence of viral infection and the chronic hepatic condition are unclear.

Asymptomatic carriers of HB, estimated to number about 900,000 in the United States, and possibly 150 million worldwide, are believed to serve as an epidemiologic reservoir for HB virus infection. Because a large percentage of patients with primary hepatocellular carcinoma are positive for the hepatitis B surface antigen (HBsAg), HB virus is suspected to be oncogenic. Because the hepatitis B surface antibody (anti-HBs) is protective against reinfection with HB virus, HBsAg purified from the plasma of chronic carriers is being evaluated as a prophylactic vaccine against HB and its sequelae.

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EDITORIALS

The Difficult Plight of Self-Employed Physicians

THE CHANGING ECONOMICS of medical practice and patient care is creating many new problems for self-employed physicians, most of whom see and treat their patients on a fee-for-service basis. When fees for service were simply a matter between physician and patient the problems were few. The fee charged related both to the skill and reputation of the physician and a patient's ability to pay. There were occasional problems with excessive charges by physicians and some inequities. However, by and large the system worked well, and provided for a wide variation in the ability of patients to pay for physicians' services—and most physicians never became wealthy.

The advent of health insurance introduced a third party into the fiscal relationship between doctor and patient. When a patient had health insurance coverage, a third party, the health insurance carrier, paid all or part of the bill and the amount and appropriateness of the physician's fee became a concern of others, that is, the insurance carrier when the money came from the private sector, or the government when it was paying the bill in a public program. As this happened it became necessary to find a way to provide the third party payors with some guidance as to what might be an appropriate fee and what might not. The solutions to this were the relative value studies and the concept of usual, customary and reasonable (UCR) fees. Both were based on the actual going rates for physicians' fees in various specialties and differing geographic areas. Provision was made for peer review and for payment of fees outside the norm by documentation of special circumstances. This worked well for a number of years, and met the needs of third party payors for guidance regarding payments, while preserving the individual self-employed physician's right to determine his or her own fees and to adjust them as necessary to rising costs or changing circumstances.

More recently the pressures on this system have been growing. Certain inequities have developed within it, and there has been some misuse, particularly when excessively high fees are charged for some of the newer procedures. Also, both government and industry are focusing more attention on physicians' fees because they pay most of them. As costs rise both are beginning to seek new means of negotiating or controlling physicians' fees as well as other costs of patient care.

Self-employed physicians now find themselves in a difficult plight. In a sense they are surrounded on all sides with no obvious way out. On the left flank, if you will, are government programs which involve fixed-fee schedules (which are apt to be inadequate) or other means to control or contain physicians' fees. On the right flank, employers in the private sector are similarly trying to develop contractual arrangements for the purchase of health care services that will control costs including physicians' fees. To the rear, the basic support of the relative value studies has been weakened if not destroyed by actions of the Federal Trade Commission, and the UCR concept is no longer working as well as it did. And the road ahead seems blocked because the labor laws are not designed to serve workers who are not in an employer-employee relationship, and any effort to act collectively outside of the protection of these labor laws is restrained by antitrust laws.

The plight seems real enough. Those who fi-

nance the greatest part of medical care, whether in government, business or industry, are possessed of economic leverage which is potentially enormous compared with that of self-employed physicians (or other self-employed professionals for that matter) who find themselves disadvantaged because there is no employer with whom they can negotiate collectively under the law. This writer believes that the time has come for new legislation that will recognize the plight of self-employed professionals, who need to be able to negotiate collectively through their professional organizations with those who actually pay for the services that these professionals render to patients or clients who have public entitlement or other third party fiscal coverage for such services. This legislation would not only be fair, but, surely, in the long range, in the public's interest as well.

—MSMW

Therapy for Acromegaly, Cushing Disease and Nelson Syndrome

THE PAPER BY Lawrence and Linfoot elsewhere in this issue, describing the effects of proton beam therapy in the treatment of acromegaly, Cushing* disease, and Nelson syndrome in 429 patients with various pituitary neoplasms, is the largest series available on the use of this technique. One of the major difficulties in determining the efficacy of therapy used in the treatment of relatively uncommon conditions such as these is the lack of availability of a large enough series of patients followed carefully for a long enough time. This study of acromegaly and of Cushing disease used a highly significant number of patients. Unfortunately, for an adequate scientific evaluation, it was not possible to follow a similar control group. The authors do present data which indicate that survival of patients with acromegaly is substantially decreased compared with the expected survival of an age-matched population. The question that cannot be answered from these data is how different the treated group may be from a nontreated group. The data presented are incomplete; for example, growth hormone levels are given for only 124 of 208 patients with acromegaly who were said to have been treated. It would be helpful if data were available to indicate whether survival was greater among those with normal growth hormone levels after therapy. Are the 10 percent who died during the course of the study those patients in whom the human growth hormone (HGH) levels were not adequately lowered by the procedure? It is of interest that there are few elevated HGH levels noted after about six years in the groups presented in their Figures 3 and 4. Was this due to continued action of the therapy over a relatively long time or the result of the death of those patients in whom levels of growth hormone had remained elevated?

There are several reports of smaller series using the alternative therapy for acromegaly, transsphenoidal pituitary surgical excision. In one recent report an adenoma was identified and removed in 27 of 28 patients; in 14 of 15 patients who were not cured by the procedure extrasellar extension had occurred.[1] In another study 16 patients underwent transsphenoidal operations for acromegaly, with satisfactory results in 12 who were followed for an average of 24 months. Failure was attributed to the possibility of locally invasive adenomas. Two patients required a second operation.[2] The authors of both of these studies concluded that transsphenoidal surgical excision is effective in the treatment of acromegaly. A third report describes 80 patients with acromegaly who had had this operation and whose cases had been followed for an average of 3.7 years. Complete regression or improvement occurred in 94 percent of the patients and tumors recurred in 5 percent. The mortality during the follow-up period was 7.5 percent.[3] From these data we must conclude that pituitary microsurgical operations for acromegaly, although effective in most cases, leave a significant number not cured.

The data presented on the treatment of Cushing disease by proton beam irradiation indicate that better survival rates occurred than were found with acromegaly. Treatment by transsphenoidal pituitary microsurgical procedures in two studies resulted in successful removal of adenomas from 16 of 18 and 17 of 20 patients; however, the follow-up period was relatively short.[4,5] In another recent review, experience with transsphenoidal pituitary microsurgical procedures for this

*THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. A explanation may be found on page 78 of the July 1978 issue.

condition was described in 24 patients, with a median follow-up of 12 months.[6] Of this group, three patients with sella destruction and one with focal sella depression were not cured; and in two patients who initially had been considered cured reoperations were required. These data, which are consistent with those obtained at this institution, point to the difficulty of identifying and totally removing microadenomas that cause Cushing disease. Although it has been suggested that pituitary irradiation prevents the development of the Nelson syndrome, other studies have indicated that this is not true.[7] Lawrence and Linfoot describe the development of this syndrome in two instances after treatment of Cushing disease with proton irradiation.

How should we, as physicians, treat our patients with these conditions? At present, therapy is probably determined to a considerable extent by the facilities available in a given area. It appears that the proton beam is an adequate form of therapy, but the data presented in the study under discussion are insufficient to allow firm conclusions. The distance that a patient is required to travel with resulting expense and inconvenience will probably continue to limit the use of this form of treatment. In those patients in whom extension of the tumor into the sphenoidal area is found or who fail to be cured adequately by the transsphenoidal approach, irradiation should be considered. It is unfortunate that neither form of therapy appears adequate for patients with suprasellar extension; therefore, early diagnosis and definitive therapy before development of such extension is highly desirable. In those patients in whom microsurgical procedures are unsuccessful for pituitary-dependent Cushing disease, pituitary irradiation and bilateral adrenalectomy are adequate alternatives.[8-10] It is important that in centers where various forms of therapy are being used to treat these potentially fatal diseases, data concerning the efficacy of each approach be collected as well as information concerning the follow-up of patients. This information should be made available to practicing physicians.

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Self-Care as a Cost Containment Measure

ONE OF THE MORE RECENT in a long line of assumptions about health care costs is that if people can be instructed and trained to take care of themselves, this will reduce the cost of health care. One is reminded of other assumptions that have received popular credence and public support, both conceptually and fiscally. Two examples are "If more health care is given to more people this will reduce costs because people will be healthier and not need so much care" and "If more doctors are trained and brought into practice an oversupply of physicians will cause them to reduce their fees and this will solve the problem of the rising cost of health care." These and other measures have so far had an effect quite opposite to what their advocates intended—they have added to the overall cost of care, although probably with a benefit of better care for more people.

Self-care is now being touted as a cost control measure. A randomized trial of the effect of a self-care book on the number of visits to physicians, recently reported in *The Journal of the American Medical Association,*[1] concluded that a large-scale distribution of this self-care book did not result in significantly less dependence on physicians for treatment of acute medical problems, even though half of the families read most or all of the book, and more than a third used it to deal with a significant medical problem.

From this study it appears that there may be a trade-off, that is, emphasis on self-care may cause some to seek help from a physician less often, while others will be newly stimulated to call upon

a physician. While self-care may not reduce health care costs significantly, it may well result in more care for more people, as indeed have some of the other unfounded assumptions about cost containment.

—MSMW

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Agreement, Suggestions and Predictions Concerning Coronary Artery Bypass Operations

MILLER AND IVEY describe their indications for coronary bypass operations in their article "Selection of Patients for Coronary Artery Bypass Operations" elsewhere in this issue. The controversy regarding bypass operations has subsided, largely because the procedure relieves angina pectoris in 90 percent of patients, with complete relief occurring in 60 percent to 70 percent of them. Further, coronary bypass operations carried out by a team that has an operative risk of about 1 percent, will prolong the lives of symptomatic patients who have obstruction of the left main coronary artery, triple-vessel or double-vessel obstruction and, possibly, the lives of some patients with high-grade obstruction of the left anterior descending artery proximal to the first septal perforator and first diagonal.

Scientific evidence to support the view expressed above is adequate except for data concerning single-vessel disease (including the left anterior descending artery). As will be discussed later, we need a longer follow-up period (maybe more than five years) and a different method of classifying single-vessel disease than is currently used to study the survival of patients with this type of obstruction. In the meantime, I recommend bypass operations for these patients if there is evidence of subtotal obstruction of the left anterior descending artery, proximal to the first septal perforator and first diagonal; poor collateral flow; good contractility of the left ventricle, and evidence of ischemia (symptoms, positive findings on an exercise electrocardiographic stress test or on an exercise thallium scan).

It has become apparent that the variables a physician must consider in determining the need for coronary bypass operations include the patient's age and symptoms, the location of the obstructing lesions, the contractile state of the left ventricle, the status of the distal coronary arteries and the presence or absence of other diseases.

Suggestions

Sufficient data exist to support the use of coronary bypass operations for treating patients who exhibit unstable angina pectoris, even if the angina subsides after the patient is admitted to hospital. The first-year mortality in such patients who are treated medically is almost 10 percent. In contrast, the operative risk in my own patients who have had bypass operations for unstable angina pectoris is 1 percent, and as yet there have been no deaths subsequently (follow-up period, one to four years).

The patients with unstable angina pectoris who are treated medically and who do not die within the first year may continue to have angina pectoris and myocardial infarctions. Unfortunately, their condition may eventually become inoperable because of severe damage to the left ventricle. Accordingly, procrastination because these patients are feeling better may be dangerous. It is also becoming apparent that the longer a physician procrastinates in such cases, the more likely it is that the patients will not return to work. Ideally, it is best to compress the period that includes initial examination, coronary arteriography, coronary bypass operation and the patient's return to work to three months—rather than the present six to eight months.

Accurate determination of the cost of medical care is very complex. Certain patients with angina pectoris spend considerable money on drugs, and many are admitted to hospital repeatedly for observation because of episodes of myocardial ischemia. Many patients spend less money on medication and hospital bills after the operation than they did before it. Therefore, it follows that for some patients, an inordinate delay may simply put off the time when less money need be spent for medical care.

If a bypass operation is done without inordinate delay, it may permit a patient to retain a job, thereby preventing him or her from seeking disability payments from the government or from private insurance, which is very costly. This expense, in addition to contributing less money to the Internal Revenue Service, makes procrastina-

tion very costly. These considerations are very important when one calculates the cost of a bypass operation.

Evidence is beginning to accrue that medical treatment and follow-up of patients who have unstable angina pectoris as a result of coronary atherosclerotic heart disease is costly. During a two-year follow-up period, the cost of medical treatment for patients who have unstable angina pectoris is about half the cost of a bypass operation. *Medical treatment for these patients over two years, which is then followed by a bypass operation is the most costly approach of all, and may cost four times as much as medical therapy alone and twice as much as the surgical therapy alone.* Remember, too, that at least a third of patients with unstable angina pectoris cannot be maintained indefinitely on medical management because of unacceptable angina pectoris.

Laboratories equipped to carry out coronary arteriography will be doing many more arteriograms during the next decade than they did during the last one. The public spotlight will shine on them and it is our responsibility to use them properly.

The current taxonomic classifications used to delineate subsets of coronary disease will change during the next decade as well. As Miller and Ivey emphasize, coronary disease is complex, and determining the need for a bypass operation according to the number of coronary arteries involved will probably give way to some sort of "jeopardy index." This index will attempt to predict the amount of ventricular muscle mass that would be lost if an infarct occurred distal to the coronary arterial obstructions noted on the coronary arteriogram.

It is very likely that coronary artery bypass operations will be shown to prolong the lives of patients with obstruction of the proximal portion of the left anterior descending artery compared with patients having this condition who received conventional medical treatment. It has long been known that little difference in survival can be shown between medical and surgical treatment during the first five years; however, it is entirely possible that the eight- and ten-year survival curves will be different.

Transluminal coronary angioplasty may be used in the operating room. Suppose a patient with unacceptable angina pectoris has 95 percent obstruction of the midportion of the left anterior descending artery and 40 percent obstruction of the proximal right coronary artery. The lesion in the left anterior descending artery cannot be reached using the percutaneous transluminal catheter technique and must be bypassed, while the lesion in the right coronary artery is not sufficiently severe to be grafted. Surely a method could be developed to carry out coronary arteriography during the surgical procedure, and the transluminal catheter could be used to dilate the early lesion in the right coronary artery. Maybe, just maybe, this would slow the progress of the disease in the right coronary artery.

New attempts will be made to alter the progress of coronary atherosclerosis by controlling diet and administering drugs. In the future, studies will be implemented in patients who have had coronary bypass operations. The idea being that such patients may now profit from this therapy whereas formerly such an approach failed because the patients died earlier and there was little chance that such extensive lesions could be reversed. Suppose the vessels distal to a bypass graft were normal at the time of the operation. Maybe a preventive approach would help these patients.

Summary

I agree with Miller and Ivey regarding the value of bypass operations in relieving angina pectoris, and that the procedure will prolong the lives of carefully selected patients with obstruction of the left main coronary artery, triple-vessel disease or double-vessel disease when the operation can be done with 1 percent operative mortality. I believe we need more data to guarantee improved survival for patients with obstruction of the left anterior descending coronary artery. In the meantime, I recommend operations in such patients with subtotal obstruction of the vessel, good contractility of the ventricle, poor collateral flow and evidence of myocardial ischemia (symptoms, positive finding on the exercise electrocardiogram or thallium scan).[1]

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CASE REPORTS

Refer to: Bennett WM, Barry JM, Houghton DC: Chronic tubulointerstitial nephritis from infectious mononucleosis. West J Med 133:248-249, Sep 1980

Chronic Tubulointerstitial Nephritis From Infectious Mononucleosis

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INFECTIOUS MONONUCLEOSIS is a relatively common viral illness with few permanent sequelae. Lee and Kjellstrand[1] in a recent review of renal involvement associated with this disease, found only a 1.6 percent incidence of serious renal disease. A single case of end-stage chronic renal failure has been reported in the literature.[2] We report a second case of chronic renal insufficiency which showed tubulointerstitial pathological changes and multiple tubular physiological abnormalities.

Report of a Case

A 12-year-old white girl was well until July 1977, when a sore throat, fever, cervical lymphadenopathy and profound malaise developed. She did not seek medical attention until six weeks later because of persistent malaise and fatigue. No antibiotics were given. Findings on physical examination were normal except for shotty cervical adenopathy and pallor. Blood pressure was 110/70 mm of mercury, with a 30 mm drop on assuming an upright posture. Pulse was 110 beats per minute. Blood urea nitrogen was 72 and creatinine 5 mg per dl; creatinine clearance was 7 ml per minute. Hematocrit was 23 percent with normal erythrocyte morphology. The leukocyte count was 4,200 per cu mm, with 62 percent lymphocytes and 2 percent atypical lymphocytes. Throat culture showed no pathogens and an antistreptolysin 0 titer was 1:24. A mononucleosis spot test was positive. Heterophile antibodies were present in a titer of 1:448. They were 1:112 after absorption by guinea pig kidney. The third and fourth components of complement were present in normal concentrations. Antinuclear antibodies were not detectable. Electrolyte studies gave these values: sodium 142, potassium 2.9, chloride 111 and bicarbonate 9 mEq per liter; calcium 8.3 and phosphate 3.2 mg per dl. Analysis of urine showed a pH of 6.5, proteinuria (2+), glucosuria (2+) and 102 leukocytes per high-power field. Culture was sterile. Total urinary protein per 24 hours was 980 mg and urinary sodium was 96 mEq per liter on a 10 mEq sodium diet. Maximum urine osmolarity after overnight dehydration was 283 with no response to exogenous antidiuretic hormone. Despite a serum pH of 7.19 and a bicarbonate value of 9 mEq per liter, urine remained alkaline with a pH of greater than 6.5. Glucose was present qualitatively in the urine with simultaneous blood sugar values of 80 percent to 90 percent. Abnormal aminoaciduria was detected by one-dimensional paper chromatography. Intravenous pyelography, cystoscopy and voiding cystourethrography showed no obstructive uropathy or evidence of renal scarring There was no family history of renal disease or exposure of the patient to drugs or toxins. The previous analysis of urine for this patient was six months before her illness, and findings were within normal limits.

Examination of a renal biopsy specimen disclosed active tubulointerstitial disease as indicated by the presence of dense inflammatory infiltrates, interstitial fibrosis and tubular atrophy (Figure 1). The inflammatory cells were predominantly large lymphocytes, but smaller numbers of plasma cells, histiocytes, neutrophils and eosinophils were also present. Mitotic figures were occasionally evident in cells of the infiltrate. Atrophy and collapse of tubules were extensive; many had become no more than cords of epithelial cells within broad, faintly argyrophilic basement membranes. Basement membranes of intact tubules were thickened and duplicated.

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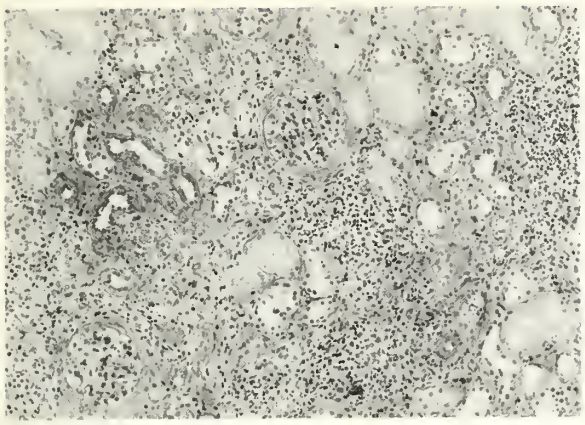

Figure 1.—Photomicrograph of a renal biopsy specimen of a patient with active tubulointerstitial disease, showing the presence of dense inflammatory infiltrates, interstitial fibrosis and tubular atrophy (reduced from magnification ×170).

Between 50 and 60 glomeruli were present in each specimen; approximately a quarter of them were completely sclerotic. Among the rest, many showed segmental capillary collapse and basement membrane thickening, but there was no evidence of specific glomerular disease. Vessels in the midst of the interstitial infiltrates were prominent because of mural thickening, but those in uninvolved cortex appeared normal.

By electron microscopic examination, glomerular and tubular changes were nonspecific. Segments of glomerular basement membranes were thickened, folded and collapsed, and mesangial matrix was slightly increased. There were no electron-dense deposits. Glomerular fluorescent antibody staining was negative for IgG, IgA, IgM and C3. C3 was present in the intimas of small vessels. Tubular basement membrane showed no immunoglobulin staining.

After volume repletion, the patient was treated with sodium bicarbonate, potassium bicarbonate and calcium supplements. She did reasonably well with conservative management for 18 months; however, progressive deterioration of renal function and development of renal osteodystrophy necessitated renal transplantation.

Discussion

Various large series of patients with infectious mononucleosis have shown approximately a 15 percent incidence of urinary sediment abnormalities,[1,3] However, renal failure has been reported in only eight patients.[1,4-8] In all instances in which pathological material is available, interstitial nephritis is prominent. Only the patient in Lowry's study[2] had chronic tubulointerstitial nephritis severe enough to require end-stage renal disease management.

The case of our patient would appear to be the second published instance of chronic renal failure associated with infectious mononucleosis. The morphologic changes were accompanied by various physiological abnormalities such as sodium wasting, inability to acidify maximally and a concentrating defect. Renal glycosuria was also noted.

The pathogenesis of the interstitial nephritis must remain conjectural. In our patient's case, no distinct immunoglobulin staining or electron-dense deposits were noted to suggest an immune complex mechanism. Lee and Kjellstrand[1] could not detect Epstein-Barr virus antigen-antibody complexes by indirect immunofluorescence. Wands and co-workers[9] found circulating immune complexes in infectious mononucleosis; however, renal disease was not present. Peters,[10] using his patient's own serum for immunofluorescence, showed viral antigen in renal tubular cells, raising the possibility of direct viral cytopathic injury. Further well-studied cases will be needed to clarify the pathophysiology of this unusual cause of chronic renal failure.

Summary

The case of a 12-year-old girl with chronic tubulointerstitial nephritis and end-stage renal failure secondary to infectious mononucleosis is reported. Renal salt wasting, renal tubular acidosis and a concentrating defect were the physiological correlates of the morphologic changes in the renal interstitium. The pathophysiology of this unusual cause of renal failure is unknown.

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Fanconi Syndrome and Oat Cell Carcinoma of the Lung

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THE RENAL TUBULAR DYSFUNCTION associated with Fanconi syndrome* is characterized by the renal wasting of circulating electrolytes, glucose and amino acids in the presence of metabolic acidosis and minimal azotemia.[1,2] In addition to the genetic causes of this malady, various acquired disorders have been identified, principally results of renal toxicity from heavy metals and orally ingested drugs, and from the disorders associated with paraproteinemias.[3,4]

This report presents an instance in which Fanconi syndrome has been related to oat cell carcinoma of the lung.

Report of a Case

A 56-year-old black woman, a domestic worker, was well until May 1976. However, progressively increasing weakness, diffuse body aches and nausea developed and she was admitted to hospital in June.

On physical examination the patient appeared chronically ill and was able to stand only with assistance. Blood pressure was 115/65 mm of mercury with the patient sitting. There was evidence of mild muscle wasting along the temporal regions, the pectoral region and the proximal musculature of the legs. Other findings of the examination were normal.

A routine x-ray study of the chest showed a left upper lobe infiltrate. The hemoglobin value was 13.2 grams per dl, the leukocyte count was 3,500 with 42 percent neutrophils and the platelet count was 98,000 per cu mm. The results of blood chemistry studies and analyses of urine are summarized in Tables 1 and 2. Bronchoscopy with biopsy showed the presence of oat cell carcinoma. Findings on brain, liver and bone scans were normal. A bone marrow biopsy disclosed infiltration with oat cell carcinoma. Electrolyte abnormalities and abnormal results on analysis of urine were noted in the initial laboratory studies, but the causes of these findings were not aggressively pursued. The patient was treated with cyclophosphamide, vincristine and methotrexate. She rapidly regained her strength and normal habitus. A complete remission was achieved approximately nine weeks after diagnosis.

The patient was readmitted to hospital in June 1977 because of weakness, lethargy, tremors, anorexia and general malaise. Examination disclosed pronounced weakness of the musculature and a diffuse tremor. No abnormalities were seen on an x-ray film of the chest and a liver scan. A bone scan showed increased vertebral uptake. Blood

*THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. A explanation may be found on page 78 of the July 1978 issue.

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TABLE 1.—*Results of Blood Chemistry Studies in Patient With Oat Cell Lung Carcinoma and Renal Tubular Dysfunction*

	June 1976	*June 1977*	*October 1977*	*November 1977*
Body surface area (sq m)	1.87	...	...	...
Plasma urate (mg/dl)	2.8	1.6	1.7	4.7
Plasma glucose (mg/dl)	76.0	54.0	45.0	86.0
Serum cholesterol (mg/dl)	258.0	221.0	218.0	254.0
Blood urea nitrogen (mg/dl)	13.0	11.0	20.0	11.0
Creatinine (mg/dl)	0.7	0.6	0.6	1.0
Serum phosphorus (mg/dl)	2.2	1.1	1.9	3.4
Serum calcium (mg/dl)	9.4	8.7	8.8	9.4
Serum albumin (grams/dl)	3.7	3.5	3.3	3.8
Serum sodium (mEq/liter)	132.0	128.0	112.0	141.0
Serum potassium (mEq/liter)	3.1	2.1	2.1	4.4
Serum carbon dioxide (mEq/liter)	19.0	17.0	18.0	25.0
Serum chloride (mEq/liter)	112.0	106.0	98.0	102.0

TABLE 2.—*Results of Analyses of Urine in Patient With Oat Cell Lung Carcinoma and Renal Tubular Dysfunction*

	June 1976	*June 1977*	*October 1977*	*November 1977*
24-hour glucose (mg)	...	570	512	224
Clinitest	1+	3+	3+	1+
Ketone	1+	1+	2+	0
Protein	1+	1+	1+	0
T_m phosphorus (% filtered load)	...	...	32%	61%
Amino acids (grams/24 hours)	...	2.2	2.6	1.4
24-hour urinary sodium/potassium (mEq/liter)	116/88	88/96	113/108	90/46
Urinary urate (mg/24 hours)	...	622	560	324
T_m PAH (mg/mm)	...	88	85	77
C_{in} (ml/mm)	...	121	106	113
C_{PAH} (ml/mm)	...	605	581	560

C_{in} = insulin clearance C_{PAH} = para-aminohippurate clearance PAH = para-aminohippuric acid
T_m = maximal tubular excretory capacity

chemistry studies disclosed a metabolic acidosis with hyponatremia, hypokalemia, hypophosphatemia and a subnormal uric acid titer. Analysis of urine showed glycosuria, proteinuria and aminoaciduria. Renal evaluation disclosed the presence of normal glomerular and tubular secretory function, although the quantities of sodium, potassium, uric acid, amino acids and glucose delivered through the urine were abnormally high. The patient was given therapy with citrate of potassium and potassium phosphate. Chemotherapy was altered to include doxorubicin and CCNU (chloroethyl cyclohexyl nitrosourea [lomustine]). Serum chemistry values improved although the urinary abnormalities persisted. The tremors and weakness subsided.

Another admission was necessitated in October 1977, heralded by diffuse muscle aches, severe weakness, headaches, cervical spinal pain and dyspnea. An x-ray study of the chest showed a mass in the left lung extending into the mediastinum. A bone scan indicated progression of osseous disease. Laboratory data mirrored those present in October 1977. Serum immunoelectrophoresis was normal. Urine immunoelectrophoresis showed no abnormal gammaglobulins. A study of urine for heavy metals showed no abnormal levels. Rheumatoid factor, latex fixation titer, lupus erythematosus preparation, cold agglutinins and C3 complement titer were normal. Additional chemotherapy was instituted with vinblastine, procarbazine and megadoses of methotrexate with folinic acid rescue. A partial remission was obtained with resolution of the pulmonary mass, lessening of bone pain, and decrease of weakness and tremors. The electrolyte abnormalities again improved when potassium citrate and potassium phosphate were given. The improved status continued until January 1978 when Gram-negative septicemia occurred during a period of pancytopenia and the patient died.

Discussion

It is uncertain whether the patient had renal tubular dysfunction antedating the occurrence of the oat cell carcinoma. However, the absence of previous symptoms, the initially normal findings on roentgenograms and the patient's initially normal habitus was inconsistent with chronic Fanconi syndrome.[1] An autopsy was not permitted, and therefore the presence or absence of an anatomic defect can only be theorized. However, it is possible that the cause of the renal tubular dysfunction was the presence of an unidentified toxin, probably produced by the neoplasm, being deposited in the renal tubular parenchyma and affecting normal reabsorptive mechanisms. Our studies of the immediate family of this patient were limited to serum electrolyte studies and analyses of urine; however, these persons are in good health and laboratory studies show no abnormalities.

Summary

A case of a patient with oat cell carcinoma of the lung and concomitant Fanconi syndrome is presented. Evidence suggests that the renal tubular dysfunction was acquired and became symptomatic during the presence of the neoplasm.

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Ureteral Metastasis in Carcinoma of the Breast

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METASTASIS FROM CARCINOMA of the breast may involve any organ of the body and it is not surprising that metastasis to the ureter occurs. The incidental finding of unusual sites of metastatic lesions in patients dying of widespread cancer is often considered of very little practical importance. However, the cases of three patients presented below illustrate that ureteral metastasis from cancer of the breast can cause life-threatening problems, and that modern treatments are effective and may lead to prolonged remission.

Reports of Cases

CASE 1. Carcinoma of the left breast was detected in a 58-year-old woman. A radical mastectomy was carried out in October 1974, followed by radiation therapy. In April 1978 the patient was admitted to Saint Joseph Hospital with a six-month history of recurrent chest wall nodules, generalized malaise and increasing fatigue. Hematologic studies showed a hemoglobin count of 6.3 grams per dl, and bone marrow metastasis was found on biopsy. X-ray studies showed extensive bony metastatic lesions, pleural effusions and hydronephrosis of the right kidney. Percutaneous antegrade pyelography was carried out, which confirmed the presence of ureteral obstruction. Cytologic examination of the fluid aspirated from the pelvis of the right kidney uncovered malignant cells felt to be typical of carcinoma of the breast. The patient was treated with diethylstilbestrol (DES). However, within a month there was evidence of progression of the disease with new cutaneous metastasis. She was then given combination chemotherapy with Adriamycin (doxorubicin hydrochloride), cyclophosphamide and fluorouracil. After five cycles of chemotherapy, a pyelogram was done following intravenous injection of contrast material; findings showed relief of the obstruction of the right ureter. In addition, the patient had complete clinical response with disappearance of cutaneous metastatic lesions and pleural effusions, and relief of bone pain. She chose to discontinue chemotherapy and, subsequently, cutaneous metastasis recurred. Treatment with tamoxifen was begun and another complete response followed and continues to date.

CASE 2. Carcinoma of the left breast was discovered in a 47-year-old woman, and a radical mastectomy was done in December 1977. On pathological examination, the axillary nodes showed no infiltration of malignant cells and estrogen receptors were not determined. In September 1978 the recurrence of chest wall nodules was noted and confirmed histologically on biopsy. Because of the onset of chills, fever and pain of the right flank the woman was admitted to Santa Ana-Tustin Community Hospital in September. Results of pyelography after intravenous injection of contrast material showed obstruction of the right ureter, which was confirmed by retrograde urography. The patient was treated with antibiotics, which resulted in prompt defervescence and relief of pain. Biopsy of bone marrow specimens and a bone scan showed metastatic lesions. Because of compromised renal function due to Goodpasture syndrome, nephrostomy was done to preserve renal function. At the time of exploration, ureteral metastasis was noted and confirmed histologically. The patient was treated with Adriamycin and cyclophosphamide, with complete remission of symptoms. A repeat pyelogram showed no abnormalities. She subsequently refused further chemotherapy. Abdominal carcinomatosis and ascites developed, and the patient died in June 1979.

CASE 3. Carcinoma of the left breast was detected in a 58-year-old man and a radical mastectomy was done in May 1974, followed by radiation therapy. In September 1976 hoarseness developed and the patient was found to have a left hilar mass. During an exploratory operation of the left side of the mediastinum, an unresectable mass was found. On histologic examination, cells from the tumor proved to be typical of carcinoma of the breast. An orchiectomy was done, with complete remission of symptoms. In May 1977 pleural effusions developed; cytologic ex-

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amination of the aspirated fluid confirmed the presence of malignant cells. He had complete remission of symptoms after intrapleural administration of bleomycin and tube thoracostomy. In June 1978 proptosis was noted, with evidence of metastasis to the right orbit, which responded to radiation therapy. The patient's serum creatinine level was elevated at 2.5 mg per dl, and bilateral hydronephrosis was noted. Subsequently, he was admitted to hospital critically ill. Findings of blood chemistry studies were as follows: potassium 8.3 mEq per liter and creatinine 4.9 mg per dl. Results of retrograde pyelography showed bilateral hydronephrosis; however, there was no focal area of ureteral narrowing. Ureteral catheter was left indwelling with complete relief of renal insufficiency. A computerized tomographic scan showed evidence of bilateral ureteral metastasis. In addition, there was recurrence of chest wall nodules. The patient was treated with cyclophosphamide, methotrexate and fluorouracil. There was partial remission of cutaneous metastasis but most important, there was complete relief of ureteral dysfunction with a normal renal function and a serum creatinine level of 1.5 mg per dl. However, in December 1978 he was readmitted to hospital with chills and fever, and died after staphylococcal pneumonia and bacteremia developed. An autopsy was not done.

Discussion

Stow[1] is generally credited with the first report in the English literature of metastasis to the ureter. He reported a patient with "fibrolymphosarcoma" with bilateral ureteral metastasis. In his discussion he indicated that ureteral metastasis had previously been described but gave no references, and a further search of the literature was not carried out. In 1929 Rathbun[2] reported a male patient with carcinoma of the breast in whom ureteral metastatic lesions subsequently developed. Fitch[3] reviewed the literature in 1976 and found 160 cases of ureteral metastasis to that time, of which 44 were from carcinoma of the breast. Abrams[4] found ureteral metastasis in 4.3 percent of 1,000 consecutive autopsies and in 7.8 percent of 167 autopsies in patients with breast cancer. Klinger[5] found only one patient with isolated ureteral metastasis from carcinoma of the stomach in the reports of 5,000 autopsies. Cohen[6] reported that in a study of 3,200 autopsies, ureteral metastasis was found in 31 patients (0.96 percent), 7 of whom had carcinoma of the breast. Geller[7] analyzed the findings of 181 autopsies of patients with breast cancer and found ureteral metastasis in 8.3 percent.

Although autopsy data indicate that ureteral metastasis is rare, occurring in less than 10 percent of patients with breast cancer, the incidence of diagnosing ureteral metastasis in patients while they are alive is exceedingly rare. Grabstald and Kaufman[8] found isolated ureteral metastasis in 12 of 6,000 consecutive cases of breast cancer. These authors found 12 other patients in whom there was ureteral involvement by direct extension from pelvic or abdominal metastasis, which they termed "bulk disease." Involvement of the ureters by direct extension is common in carcinoma of the cervix, prostate, bladder and rectum and should be distinguished from isolated ureteral metastasis.

Although most patients will have extensive metastasis to other organs at the time ureteral involvement is discovered,[9] ureteral obstruction may be the presenting symptom or the first indication of metastasis.[10]

Symptoms

Ureteral metastasis commonly causes no symptoms. Back pain occurs in approximately half of patients, and a third of them will have hematuria.[11] Grabstald[8] stated that most patients had urinary frequency, polyuria, oliguria or uremia. Of our three patients, one was asymptomatic, one presented with uremia and one had pain of the right flank, chills and fever.

Diagnosis

The diagnosis is made by contrast urography which may be excretory, antegrade or retrograde. The characteristic radiographic finding is isolated narrowing of a one- to three-inch segment of the ureter, with proximal hydroureter and hydronephrosis.[12] The narrowing may be smooth or asymmetric and there is no displacement of the ureter. There may be diffuse involvement or only hydroureter without focal narrowing, as there was in our third patient. Any portion of the ureter may be involved, and bilateral involvement occurs in from 47 percent to 100 percent of cases.[1,7-9] Findings of cytologic studies of urine are infrequently positive because mucosal involvement is not common. We noted that in the first patient, aspirated urine from the renal pelvis was positive for adenocarcinoma although the woman had no urinary tract symptoms nor hematuria. Fine-

needle aspiration biopsy in the region of the ureteral obstruction is recommended in patients with direct extension from pelvic or abdominal metastasis.[13]

Pathology

Ureters may be involved by direct extension from extensive pelvic, abdominal or retroperitoneal tumors ("bulk metastases").[8] This is most common in carcinoma of the cervix, bladder, prostate and rectum, but it is also as common as isolated ureteral metastasis in patients with breast cancer. Isolated ureteral metastasis may involve any or all layers of the ureteral wall, but is most often periureteral. The terms periureteral and ureteral metastasis are used interchangeably. Multiple segments may be involved and diffuse involvement is found in 38 percent of cases[9]; bilateral involvement occurs in most patients. Other evidence of metastatic disease may be found in as many as 90 percent of patients.[9]

Mechanism of Obstruction

Metastatic tumors may mechanically obstruct the ureter by direct extrinsic pressure, by encasement and concentric occlusion, by vigorous fibroblastic reaction or by fibrosis with traction resulting in obstructive angulation. Hydroureter may result from decreased peristalsis secondary to edema or to interference with innervation or blood supply.

Treatment

Although many patients are asymptomatic, ureteral obstruction may be the cause of severe and life-threatening symptoms. In these patients the recommended procedure is ureteral catheterization.[14,15] Newer ureteral catheters or stents are well tolerated and may be left in place for prolonged periods.[14] Nephrostomy and ureterostomy may be indicated if the ureteral catheter cannot be passed. Nephrectomy is only rarely required. Radiation therapy has been used,[16] but urinary diversion provides much more rapid relief. Most patients will have other evidence of metastatic disease and systemic therapy is required. Systemic therapy in this situation is identical to that for metastatic breast cancer without ureteral metastasis.[17] In patients in whom estrogen receptors are present in malignant cells, or in patients who have had a previous response to hormonal manipulation, additive or ablative hormonal therapy would be the treatment of choice. For patients in whom the presence of estrogen receptors in the malignant cells is unknown, for those in whom estrogen receptors are missing, or for those in whom previous hormonal therapy has failed, systemic chemotherapy will be the treatment of choice. It is to be noted that our three patients had excellent responses to combination chemotherapy, and one has had prolonged remission of symptoms while receiving hormonal therapy.

Summary

In three patients with carcinoma of the breast, ureteral metastasis was subsequently detected. The two women had unilateral and the man had bilateral ureteral involvement. All three patients had relief of ureteral obstruction in response to chemotherapy.

Ureteral metastasis is found on necropsy in less than 10 percent of patients with breast cancer, and it is only rarely diagnosed while patients are alive. Ureteral obstruction may cause severe and life-threatening symptoms that can be relieved by treatment. The clinical courses of the patients in the case reports presented illustrate the need for awareness of the possibility of ureteral metastasis.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Prevention of Pack Palsy

To the Editor: This is to report a device that conceivably will reduce the incidence of pack palsy in backpackers. In the June issue Dr. Guy Corkill and associates[1] noted that pack palsy affects the upper trunk of the brachial plexus or the peripheral nerve supply to the shoulder girdle. It is caused by pressure from back straps.

A simple modification of the pack frame should be of interest to all physicians concerned with this problem. It is proposed to add to both sides of the bottom support of the frame a lateral horizontal forward extension appropriately shaped (Figure 1). Both arms, fashioned from aluminum tubing, cantilever forward past the side of the trunk. They provide a grip for both hands, and when the backpacker bears down on them they will tilt the top of the frame forward. This will relieve immediately the continuous pressure against the frontal shoulder area. Occasional lifting of the grip will modify the pressure to which the sensitive trapezio-scapular region is subjected.

Figure 1.—View of the pack frame to which side extensions have been added. They permit shifting of the load on the shoulders. Straps have been omitted in the sketch.

During years of family backpacking trips I experimented with what I had called the Schmerl grip and have found it indispensable because it allows one to lighten the pack weight occasionally. During long hikes, I might add, it gives the dependent arms a chance of restful support and an intermittent active role. Subjectively, a pleasing sensation of relief in the upper extremities suggests, perhaps, hemodynamic variations due to such changes in pressure.

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Treatment of Heat Stroke

To the Editor: Recently on the CBS Evening News, a heat-stroke victim was shown being given the recommended ice treatment[1] at a famous Dallas hospital affiliated with a distinguished medical school. The external application of ice is the wrong treatment for heat stroke. It aggravates the process it is meant to allay. By its vasoconstrictive effect on skin arterioles, it actually interferes with the normal process of heat loss through the skin, which the body in its superior physiological wisdom is trying to accomplish. However, it is gratifying to the physician to feel the iced body cool to his touch without disturbing him to inquire into the underlying physiology.

Evaporative cooling should be considered as a better alternative.[2] First, treat the life-threatening hypovolemic shock and the associated electrolyte deficiencies and imbalances; then lay the naked patient on a rubber or plastic sheet, wrap him in another of cotton continually doused with water and go about the careful examination of the patient for heart trouble, infection or other causes which may have made him more susceptible to the effects of heat. As circulation is restored the

cooled blood is returned to the internal organs with beneficial effect. Fans can be used to hasten the process of evaporation.

The patient given the ice treatment in Dallas died the following day.

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Commentary on Male Impotence

To the Editor: Recently, an article entitled "Impotence Is Not Always Psychogenic" by Spark, White and Connolly appeared in *The Journal of the American Medical Association.*[1] Considerable publicity was given this report in local newspapers (and, I presume, in the lay press nationally). Some of the implications that a lay or professional reader might glean from a cursory glance at the article impel me to write a brief constructive criticism, especially in view of some imperious demands for and assessment of serum testosterone level (and even some clinically questionable need for skull x-ray studies in search for a pituitary tumor) that have come to my attention since the above mentioned study was published.

As a result of my interest during the past 25 years in male psychogenic impotency, I have reported a technique of "urologic" counseling as treatment. To date, more than 300 men with impotency have been evaluated by me on a one-to-one basis. In our 1975 report of 62 such men, we found that more than 90 percent achieved satisfactory restoration of sexual function generally after three weekly sessions.[2] Our more recent report emphasized that, even in the presence of organic illnesses, including diabetes mellitus, or major vascular disease, and of operations such as radical prostatectomy, urologic counseling could aid in reinstatement of sexual function.[3] Thus far I have not assembled my data as to the exact percentage of successful recovery of sexual potency after urologic counseling.

In 1959 my colleagues and I defined sexual potency as "psychologic desire for coitus which produces penile erection adequate for intromission and climax."[4] Frequency of intercourse was specifically excluded from that definition. In the current paper by Spark and co-workers, who quoted Masters and Johnson's definition of impotence as greater than 25 percent erectile failures during attempted intercourse, six of seven men in their hypergonadotrophic-hypogonadism group were said to have engaged in successful intercourse "relatively infrequently" and ". . . episodes of failure caused major embarrassment." For purposes of uniformity, investigators should agree upon a definition and arrange case groupings without variations. Interjection of emotional factors ("embarrassment") clouds the issue. In addition, there is fundamental objection to combining *primary impotency* (never having had sexual experience) and *secondary impotency* in a single group.

Spark and his colleagues commendably reported that determining the serum testosterone level is a valuable step in the study of an impotent patient for the purpose of diagnosing ". . . a surprisingly high incidence of abnormalities of the hypothalamic-pituitary-gonadal axis." However, the conclusion that serum testosterone level may be diagnostically definitive must be challenged since it is well known that men with either normal or low serum testosterone level may be potent or impotent. Indeed a low testosterone level in an impotent man raises the question as to whether it precipitated the impotency or, on the contrary, was a consequence of sexual inactivity. Of the 105 patients in Spark's report, 68 had normal serum testosterone levels.

These authors found low testosterone levels in 37 men never previously evaluated by hormone studies. Among these patients many had significant endocrinopathies: 10 of 20 in the hypogonadotrophic-hypogonadism group had pituitary tumor. Physiologic effect of and subjective impact upon a man with pituitary tumor could well impair libido and potency per se, as would also apply to two other of their patients who had brain tumors and another who suffered pure red blood cell aplasia.

The presence of small or soft testes mentioned by Spark and his colleagues does not necessarily have clinical significance. Furthermore, castration has been performed in countless men with advanced prostatic cancer as a therapeutic step—and many of these men continued to perform sexually despite the debilitating effect of prostatic cancer.

With regard to diabetes mellitus, this writer is far more impressed with those 50 percent to 60

percent of diabetic men who retain their potency than in those allegedly impotent because of their disease. It is well known that potency may be retained, or impotency may develop in a diabetic man without correlation with the severity or the control of the disease. Testosterone therapy alone, or with chorionic gonadotrophin, has not been successful in overcoming impotency in diabetes, according to Kolodny et al.[5]

None of Spark's patients received any placebo. A double-blind study would be very important, particularly since I have learned from my clinical experience that many instances of transitory response (if any at all) to "potency medication" result from a three-way interaction, namely, the quests of an *expectant patient* for help from a purportedly *knowledgeable physician* who gives an *allegedly useful medication*—rather than from any pharmacodynamic effect of the medicine itself.

In a lengthy review of the relationship of hormones to aging, Davis concluded that ". . . loss of sexual potency is so complex a process that it is not justified to attribute it primarily to decreased androgen production."[6] I agree.

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Triamcinolone and Keloids

To the Editor: The epitome of progress "Triamcinolone for Hypertrophic Scars and Keloids," which appeared in the July 1980 issue, merits comments.

Like Dr. Brody, I believe that intralesional injection of triamcinolone is the best currently available treatment for keloids. However, there are three, not two, commercially available respiratory triamcinolone injection materials. Triamcinolone hexacetonide was not mentioned. This salt is the least soluble, and therefore the longest acting of the respiratory triamcinolone preparations on the market. Intralesionally given corticoids are widely used in dermatologic practice. Like most dermatologists, I prefer triamcinolone acetonide (Kenalog). However, I am not aware of any studies comparing the efficacy of the acetonide with the hexacetonide salts in the treatment of keloids.

Triamcinolone acetonide persists in tissues—and therefore has a period of action of three to four months; not the "up to four or five weeks" claimed by Dr. Brody. This is of practical significance; the maximum keloid regression will usually be observed toward the end of this period, and therefore patients should be seen at three- to four-month intervals.

Dr. Brody suggests that the injections may be either preceded by local infiltration of lidocaine or else the triamcinolone suspension may be mixed with local anesthetic before administration. The latter alternative is poor advice. Triamcinolone acetonide—unlike lidocaine—does not by itself sting on injection. The discomfort of injecting keloids without anesthesia is due to a combination of needle prick pain, plus the pain of injecting fluid under pressure. These are instant, but brief, pains; adding lidocaine to the suspension only adds the lidocaine "sting." If a 30-gauge needle is used, injection into small keloids can usually be done without anesthesia. With large keloids, or when the patient is sensitive, Dr. Brody's first suggestion of preliminary infiltration with lidocaine is the appropriate procedure.

Dr. Brody mentions side effects without clearly distinguishing between local and systemic ones. I would disagree with the arbitrary statement that "The maximum dosage is 60 mg. (1.5 ml) every 30 days." This amount of triamcinolone acetonide once a month will completely suppress endogenous corticoid production, and also cause significant systemic effects. Atrophy is the main local side effect—it is of course recognized that atrophy of the *keloid* is the aim of treatment. Too concentrated a corticoid, or too superficial an injection, will lead to *epidermal* atrophy which can cause a very unsatisfactory result. Epidermal atrophy is more likely to occur with the 40 mg per ml triamcinolone acetonide formulation (Kenalog-40), and that is why I usually start with the 10 mg per ml injection.

A few words about the technique of injection. A fine needle (30-gauge) on a tuberculin syringe equipped with a Luer lock should be used. It takes pressure to get the material into a keloid. The in-

jection is *not* intradermal, but intralesional, at a depth of 3 to 7 mm, sometimes more in the case of a thick keloid. The injections should be spaced about 1 cm apart, and only a small amount—about 0.05 ml—injected at each site.

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Medicaid in California

To the Editor: I read the article by Beverlee Myers, "Medicaid and the Mainstream: Reassessment in the Context of the Taxpayer Revolt" (West J Med 132:550-561, Jun 1980), with much interest, especially with regard to the various ways the Department of Health Services is going to control the costs of the Medi-Cal program. However, there is no mention of the cost-effectiveness of the proposed program. I also have not come across any reference relating to the administrative costs of running the California Medicaid program (Medi-Cal). I have heard that the administrative costs for the Medi-Cal program run as high as 50 percent (estimated by the Little Hoover Commission). I would like to know if Ms. Myers would like to comment on this.

KELVIN LOH, MD
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* * *

Ms. Myers Replies

To the Editor: In response to Dr. Loh's question regarding the cost-effectiveness of the proposed Medi-Cal Restructuring Plan, the Department of Health Services has estimated these reforms would achieve cost savings of approximately 15 percent to 20 percent at the end of a five-year implementation period.

As for Medi-Cal's administrative costs, direct administrative costs are approximately 7.3 percent of total program costs, or about $300 million annually (not counting administrative costs of providers which are included in their payments). A little over half of this administrative cost (55 percent), about $150 million per year, is incurred determining and redetermining eligibility for Medi-Cal benefits; 25 percent is related to fiscal intermediary operations—the process of paying provider claims for services to Medi-Cal beneficiaries; 7 percent is allocated to field services and recovery activities (prior authorization of certain expensive Medi-Cal services, such as inpatient hospitalization, and recovery of funds inappropriately paid by the program); 5 percent is incurred by audits and investigations, and the remaining 8 percent supports all other functions.

The Little Hoover Commission's estimate in 1976 that total administrative costs *may* approach 40 percent went beyond the direct administrative costs discussed above. In addition, it included estimates of provider administrative costs and assumptions about large amounts of program overuse and fraud and abuse by providers and beneficiaries. Such estimates and assumptions are not generally included in the calculation of health insurance administrative costs.

Medi-Cal's 7.3 percent direct administrative cost compares very favorably with those of private health insurance organizations. As reported in the *Statistical Abstract of the United States*—1979, published by the United States Department of Commerce, private health insurance organizations' administrative costs were 12.8 percent of their premium income in 1976. If Blue Cross/Blue Shield is excluded, this figure rises to 18.9 percent.

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County Hospitals, Medi-Cal and Programs of Reform

To the Editor: I was glad to see the perspective of Beverlee Meyers and Rigby Leighton ("Medicaid and the Mainstream: Reassessment in the Context of the Taxpayer Revolt") in the June 1980 issue. As one who has been a student in and employed by various county hospitals in California for 12 of the last 16 years, primarily serving the Medi-Cal (California's Medicaid program) population, I would like to offer some comments from that perspective.

First, Myers and Leighton speak of legislative and administrative "attempts to limit participation to efficient facilities." They are, I believe, referring to attempts to restrict hospital admissions primarily to county hospitals. County hospitals are strapped with facility, administrative and personnel problems that make them very unlikely candidates for restructuring their medical care delivery systems to become less costly if reorganized in this manner. Medi-Cal at present reimburses a private provider about $10 for a brief office visit. It reimburses hospital outpatient clinics about three times more than this (and emergency rooms are reimbursed even more) for the same level of

service. Shifting care further to county outpatient facilities, the way they are currently structured, might very likely lead to an increase in the cost of care.

The same point can be made about Short-Doyle Medi-Cal, which, for example, may pay a county mental health center $50 for an outpatient visit, regardless of the level of professional training of the provider, while paying a licensed psychologist in the private sector just under $25 to see the same patient. Only Short-Doyle Medi-Cal funded agencies can be paid for the services of nonlicensed personnel. In the private sector, only licensed psychologists and psychiatrists are legally eligible for reimbursement. Here is a specific example in which the current system encourages potentially lower quality at over twice the cost.

Another example of the subtleties of inefficiency is California Assembly Bill 8 (passed in 1979) in which the state reimburses a county for over half of the deficit of their county hospital. This legislation had minimal incentives for efficiency: the larger a hospital's deficit, the greater the handout. This kind of reward for inefficiency on one side (public sector) with increasing control of overpayments on the other side (private) makes me think that when cleaning its own house, the state is more concerned about supporting counties than it is about costs of medical care. This may be a worthwhile goal, but it should be addressed as such and not disguised as Medi-Cal reform.

It is obvious from the Meyers-Leighton article that the annual expenditures per eligible enrollee in Medi-Cal has grown at a rate significantly less than of inflation, and that the main reason for the large increases in the Medi-Cal budget has been to expand the number of people covered (and this may be reasonable in post-Proposition 13 times, in order to shift the tax burden away from the counties to the state). In that context, the current cost of the Medi-Cal program may not be unreasonable. I doubt very much, however, given the constraints of county health care systems, that any alternative based on their exclusive use, given the same number of people, is going to be less expensive than one based on achieving a competitive balance between the public and private sectors.

I agree with the authors about many of the problems of Medi-Cal, and I agree with their underlying emphasis on prepayment and financial incentives for efficiency. Other potential ideas for cost savings that were not addressed in the article include health education for appropriate use of services, copayment by beneficiaries, decreasing use of emergency rooms, increasing alternatives to skilled nursing facilities, providing mainstream care through established health maintenance organizations and decreasing administrative costs. Overall, when considering that health care is now properly viewed as a right, I feel Californians have gotten a lot for their money through Medi-Cal. Before returning to a more two-tier health care system, I would want to see some documentation and careful study showing that it would, in fact, decrease costs without lowering quality, and that the goals of saving county hospitals and reforming Medi-Cal are separated where need be.

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Refer to: Babb RR: An evaluation of the executive health examination (Health Care Delivery). West J Med 133:260-263, Sep 1980

An Evaluation of the Executive Health Examination

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During a one-year period 420 middle-aged patients were examined as part of the executive health program at the Palo Alto Clinic. Of these, 30 percent were found to have at least one disease and 20 percent to have at least one laboratory abnormality. It is concluded that such examinations are worthwhile, especially in identifying self-destructive habits and serious emotional illnesses in busy, highly motivated executives.

THE CONCEPT that one can prevent disease and maintain health by participating in an annual or periodic physical examination program is under attack.[1-3] Critics point out the high cost of such examinations and associated low yield of life-threatening diagnoses. Self-destructive habits such as smoking, alcohol abuse and overeating are difficult to change.[4] Screening laboratory tests are plagued with false-positive results, are often misunderstood, and often are ignored by both doctors and patients.[5-9] We are told that "most illnesses, especially the major ones, are blind accidents that we have no idea how to prevent."[1] Furthermore, health professionals tend to "oversell prevention, to overestimate their ability to deal effectively with detected disease, and to overvalue the benefit of their care to patients."[2]

Despite these criticisms, corporations continue to invest considerable effort and money in executive health programs. Past reviews of the health benefits derived have been favorable. For example, Carryer and colleagues concluded that "such care does permit the prevention, arrest, reversal, and cure of certain diseases and can promote the health and well-being of the subject and decrease his risk of morbidity and early mortality."[10]

Very few clinics with executive health programs have published results from which one can make judgments as to a plan's worth. Thus, a review of my experience seems both timely and useful.

Executive Health Program at the Palo Alto Clinic

The Palo Alto Clinic (Palo Alto, California) has sponsored an executive health program for more than 30 years. At present more than 100 corporations, mainly involved with finance, retailing or electronic equipment manufacture, send top management employees voluntarily through the program every one to two years. The examination takes one day and includes history, physical examination and laboratory tests including blood count, analysis of urine, VDRL, 12-channel panel —SMA 12/60 (calcium, phosphorus, glucose, blood urea nitrogen, uric acid, cholesterol, albumin, total protein, bilirubin, alkaline phosphatase, lactic dehydrogenase and serum glutamic oxaloacetic transaminase), T_4 thyroid test, triglyceride, an x-ray study of the chest and electrocardiogram. Tests such as glaucoma screening,

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pulmonary function, proctosigmoidoscopy and the exercise electrocardiogram are often, but not always, done. Most corporations allow further diagnostic evaluation if deemed necessary by the examining doctor.

Cost of the above program varies from $250 to $350 per examination. The results are discussed with each patient by phone, mail or in person depending on his or her wishes and availability.

Population Studied

To avoid interobserver variability I reviewed all the records of executives seen by a board certified internist (the author) over a one-year period.

TABLE 1.—*Age Groups of 420 Patients in Executive Health Program*

Ages of Patients (Years)	*Number of Patients*
20-30	6
30-40	99
40-50	157
50-60	130
>60	28
TOTAL	420

TABLE 2.—*Diagnoses in 420 Executives*

Disease	*Number of Patients**	*Percent of Patients*
Obesity†	33 (5)	8
Hypertension	24 (20)	6
Depression	17 (3)	10
Alcoholism‡	14 (6)	
Anxiety	10 (4)	
Arthritis§	12 (8)	3
Inguinal hernia	8 (8)	2
Glaucoma	6 (6)	1.5
Miscellaneous	20 (17)	5

*Parentheses show number with new diagnosis.

†Defined as a weight greater than 20 pounds over "ideal" by Metropolitan Life Insurance tables.[11]

‡Criteria for alcoholism are those recently published by the National Council on Alcoholism.[12] In these 14 patients, diagnosis was based on the amount consumed, the behavior patterns showing psychological dependence on alcohol, or a combination of both.

§Diagnosis based on physical findings in the hands (7), and x-ray studies of the spine (2), hips (2) and knees (1).

Of the 420 persons examined, most were men (403 of 420), white, middle-aged, college-educated and in positions of considerable responsibility. Age groups are given in Table 1.

Results

As can be seen in Table 2, 30 percent of these executives were found to have at least one disease. Diagnoses included obesity in 33, serious emotional illnesses in 27, alcoholism in 14 and hypertension (blood pressure greater than 160/90 mm of mercury) in 24. Other disorders were degenerative arthritis (12), inguinal hernia (8), prostatic hypertrophy (6), skin cancer (5), glaucoma (6), heart murmur (3), angina pectoris (3), hiatus hernia with esophagitis (2), cataracts, diverticulosis, celiac sprue, cholelithiasis, peptic ulcer (5), goiter, nephrolithiasis and sarcoidosis.

Patient awareness of their diseases varied. For example, most of those who were obese knew it, and had attempted to lose weight by a variety of diets. Although a few with hypertension had been told of "high blood pressure" in the past, none were receiving treatment or understood the serious implications of this diagnosis. Most of those with serious emotional illnesses admitted to the same only after appropriate and nonthreatening questions were asked (see below). The other listed diagnoses were new ones in virtually every case (Table 2).

Laboratory screening tests detected abnormalities in 93 of the 420 patients (20 percent). These mainly consisted of minimal to moderate elevations in serum cholesterol, triglyceride, uric acid or bilirubin values (Table 3).

Eleven pulmonary function tests gave abnormal findings, ten of them in heavy smokers. Only two electrocardiograms (minor arrhythmias) and one x-ray study of the chest (bilateral infiltrates later diagnosed as sarcoidosis) showed abnormalities. Ten of 230 patients (about 5 percent) having

TABLE 3.—*Abnormal Results of Screening Tests in 420 Executives*

Test	*Normal Values*	*Number of Patients With Abnormal Values*	*Range of Abnormal Values*
Cholesterol	150-250 mg/dl	22	270-345 mg/dl
Triglyceride	less than 165 mg/dl	17	180-440 mg/dl
Uric acid	2.5-8.0 mg/dl	17	8-10.2 mg/dl
Bilirubin	0.2-1.2 mg/dl	15	1.5-3.2 mg/dl
Glaucoma screening	...	6	...
Analysis of urine	...	4	...
Miscellaneous	...	18	...

TABLE 4.—*Poor Health Habits Identified in 420 Executives*

Habit	*Number of Patients*	*(Percent)*
Sedentary life-style	200	(48)
Smoking	108	(26)
Obesity	33	(7)
Alcohol abuse	14	(3)
Drug abuse	0	(0)

routine proctosigmoidoscopy were noted to have small polyps; all polyps were benign on removal.

Poor health habits[4,13] identified in the 420 patients are given in Table 4.

Patient Compliance

I had examined and counseled 218 of the 420 patients in years previous to this study, and thus could ascertain how many had been able to change poor health habits. Five of the 14 obese patients had managed to lose at least 10 pounds of weight, 12 of 48 had stopped smoking, 6 of 8 were abstaining from alcohol and virtually all felt they were more physically active. Fourteen of the 20 patients with depression or chronic anxiety, on my advice, received counseling in the interim and felt considerably improved.

Discussion

The annual or periodic health examination has become an important component of American health over the past 100 years.[14] It has become increasingly clear, however, that the mere establishment of a diagnosis may be of little real benefit to a patient.[2] Reviews of executive health programs have been generally favorable, but this has been based on listing many new diagnoses.[10,14-17] Results of my review agree in general with those previously cited. For example, 20 percent to 30 percent of executives are obese, 10 percent to 20 percent have hypertension and another 5 percent to 20 percent show signs of arteriosclerotic heart disease. In contrast to my findings, earlier studies have barely mentioned emotional illness. The discovery of cancer, other than of the skin, is uncommon.

Because the 420 executives examined cannot be compared with a control group, I am unable to say with certainty that their executive health examination will lead to less future morbidity and mortality. Nonetheless, the discovery of hypertension, emotional illness and other diseases, combined with the changing of poor health habits in some, allows me to feel that the overall results will be beneficial. Carryer and colleagues[10] after reviewing results of 2,812 examinations on 569 executives seen at the Mayo Clinic over 24 years felt likewise. Two large groups of middle-aged adults were followed-up for 7 to 11 years in a Kaiser-Permanente health plan.[18,19] Those having regular examinations had less "potentially postponable" causes of death such as cancer, hypertension, and stroke as compared with those in the control group.

The value of laboratory screening tests, as well as which ones to include in executive health programs, is still uncertain. One can list abnormal values derived from such testing, but the importance of such results to one's future health is not clear.[5,6,9] Moreover, abnormal results may be falsely positive, especially when the disease being screened for is uncommon.[7,20] Finally, there is considerable debate about the desirability of even treating such laboratory "diseases" as hyperlipidemia or hyperuricemia. All of the patients with hyperlipidemia listed in Table 3 were treated by diet alone. The highest uric acid determination was 10.2 mg per dl, and none of the 17 patients with hyperuricemia were felt to require drug therapy. The hyperbilirubinemia was minimal in all, and did not indicate clinical evidence of liver or biliary tract disease. Other screening tests, especially pulmonary function tests, x-ray studies of the chest and electrocardiograms, in this population of asymptomatic men were of little benefit.

With the above considerations in mind, can one justify an executive health program? My answer is a qualified yes and depends on the goals one hopes to achieve by such programs.

Certainly *risk factors* can be identified, and perhaps future disease can be prevented. There is some evidence that good habits promote health and allow patients to feel better.[13,15,21] Although as noted by Burnam[4] only 10 percent to 30 percent of those with self-destructive habits such as smoking, overeating and alcoholism can change, at least a start can be made via the periodic examination. Much depends on the doctor-patient interaction and art of communication.[22]

Diseases can be identified, treated and at times cured. I have been impressed by the opportunity in this executive health program to uncover serious emotional illness, especially depression. Executives often live under constant stress,[23] and seem relieved when asked to discuss this aspect of their lives in the privacy of a doctor's office. I have

found many to suffer from marital discord,[24] loneliness, overwork[25,26] and sexual dysfunction,[27] but they have to be asked, rarely volunteering this information. Those with hypertension and the numerous miscellaneous diseases noted above are now under appropriate management. Of these, 14 were advised to have operations: five with skin cancer, six with large or symptomatic inguinal hernias, two with significant prostatism and one with gallstones.

Corporations have been satisfied with our program. It is of interest that most have not asked for reports of specific results, and thus individual "privacy" has not been an issue. Moreover, when an attempt was made by me to decrease the number of screening tests, executives were often upset, and their companies asked that the program not be changed.

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The Rocky Mountain Center for Occupational and Environmental Health

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The Rocky Mountain Center for Occupational and Environmental Health, established at the University of Utah in 1977, has developed innovative training programs in occupational and environmental health, and an administrative structure that may assist other universities as they develop multidisciplinary programs in the field of occupational health and safety.

In 1977 the Rocky Mountain Center for Occupational and Environmental Health (RMCOEH) was established at the University of Utah in Salt Lake City. The Rocky Mountain Center provides occupational and environmental health training, research, and service to the Rocky Mountain states. There were several advantages in choosing Salt Lake City as the location for such a center: (1) it had served as a focal point for occupational safety and health (Occupational Safety and Health Administration [OSHA] analytical laboratories, OSHA Health Response Team, National Institute for Occupational Safety and Health [NIOSH] analytical chemistry contract laboratory, and industrial hygiene facilities and personnel of Kennecott Minerals, American Smelting and Refining, and Radian Corporations); (2) it had the resources of the University of Utah centrally located on one campus (Colleges of Mines, Engineering, Medicine, Nursing, Law, and so forth); and (3) the Department of Family and Community Medicine had the components of a School of Public Health (Master of Science in Community Medicine, equivalent to a Master of Public Health, and preventive medicine and public health residencies).

A NIOSH Educational Resource Center grant was awarded in 1978 and provides most of the financial support. It funds practically all of the training activities, whereas research monies are obtained from private, state, and national sources. RMCOEH is one of 12 NIOSH Educational Resource Centers.

The purpose of the Rocky Mountain Center is fourfold: (1) to reduce workplace-related disease and injury by training occupational safety and health professionals and by carrying out research to develop the pertinent scientific information from which action can be taken, (2) to work with and assist both industry and labor in identifying and defining occupational and environmental

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ABBREVIATIONS USED IN TEXT

DFCM = Department of Family and Community Medicine
MSCM = Master of Science in Community Medicine
NIOSH = National Institute of Occupational Safety and Health
OSHA = Occupational Safety and Health Administration
RMCOEH = Rocky Mountain Center for Occupational and Environmental Health
USU = Utah State University

TABLE 1.—*Master of Science in Community Medicine (MSCM)*

	Credits
Core Requirements:	
Environmental Health Problems	3
Introduction to Biostatistics	3
Epidemiology	3
Health Care Organization	3
Social Context of Health Care Systems	3
Biostatistics/Study Design	3
MSCM Seminar	3
	21
Occupational-Environmental Health Track:	
Occupational Lung Disease	3.0
Biochemical Toxicology	5.0
Fundamentals of Industrial Hygiene	3.0
Industrial and Mining Safety	3.0
Interdisciplinary Seminar in Occupational Safety and Health	1.5
	15.5

health problems, (3) to develop an awareness of environmental problems through education, and (4) to develop innovative ideas for the role and training of occupational safety and health professionals to advance the specialty in academia, in the workplace and in the community.

Training Programs: Occupational Medicine

The occupational medicine residency/fellowship is a two-year program, established in July 1978. The residency provides didactic, research, clinical and practical training. The first year involves completion of the Master of Science in Community Medicine (MSCM), an accredited degree program. The MSCM requires 60 quarter credit hours, including core, track, thesis and elective courses. The core requires 21 course credits, the occupational-environmental health track requires 15.5 credits, and the thesis is 15 credits allowing 8.5 or more credits for electives. Table 1 illustrates the core requirements and the occupational-environmental health track. Recommended electives include courses in air pollution, management, advanced statistical methods in epidemiology and advanced topics in occupational medicine. In addition, the residents may elect the industrial hygiene track, which provides a unique opportunity to learn industrial hygiene. The occupational medicine residents, nurses and industrial hygiene students all participate in the weekly interdisciplinary seminar in occupational safety and health.

Research during the first year includes course work that teaches the skills of writing a research grant or contract. The second year emphasizes research, with each resident designing, conducting and analyzing data from a research project (usually a field survey). The research thesis should be of publishable quality as a manuscript in a refereed journal. The residents are also strongly encouraged to write a review paper during their residency.

Clinical training includes working in an occupational medicine clinic and clinical rotations in pulmonary disease, neurology and dermatology. The Occupational Medicine Clinic, held twice weekly, is a referral resource for the Intermountain area. Workers with occupational diseases or complex exposure histories are usually seen. The residents also have a two-month clinical rotation on the pulmonary consulting service of one of the University of Utah-affiliated hospitals. Training in establishing differential diagnoses of chest disease is considered important for occupational medicine physicians. Up to two additional months may be spent in one of the pulmonary function laboratories to obtain skills in carrying out and analyzing pulmonary function tests. Dermatology clinics are taken during both years to learn how to diagnose, treat and prevent occupationally associated dermatoses.

The practical training is highlighted by a two-month preceptorship during the second year, which is divided between industry and labor. Each resident learns to appreciate their often divergent viewpoints, gains administrative skills, and is expected to investigate an extant problem during the preceptorship. Examples include Mountain Bell, Thiokol, Hercules, United States Steel-Geneva Works and Johns-Manville Corporation for industry; the AFL-CIO in Utah or Washington, DC, or the Oil, Chemical and Atomic Workers Union (OCAW) for labor, and governmental agencies, such as the

OSHA Health Response Team, OSHA headquarters in Washington, DC, or the Utah Department of Health. Residents may also work with specific persons, such as Geno Saccomanno, MD, PhD, in Grand Junction, Colorado, who offers training in uranium miners' health and in sputum cytology.

The residents also participate in NIOSH Health Hazard Evaluations (HHE). In the HHE program, each resident carries out a plant walk-through (initial observation of the manufacturing process and control methods), subsequent medical examination of the workers, and writes the final report under faculty supervision. The residents participate in all of the field research to the extent feasible at the RMCOEH. Chest radiographs from the surveys are interpreted according to the 1980 International Labor Organization Classification of the Radiographs of the Pneumoconioses by a consensus reading of the Rocky Mountain Center's three NIOSH-certified B readers.

The residency has received preaccreditation status by the Graduate Medical Education Committee of the American Medical Association. Following completion of the program, the residents are eligible to take the occupational medicine examination of the American Board of Preventive Medicine.

Table 2 outlines the two combined training programs that are available. A four-year combined program with family practice and occupational medicine leads to dual board eligibility. The first two years are in family practice; the third year is divided, with fall and winter quarters spent in the MSCM didactic program and the summer and spring devoted to family practice; the fourth year is entirely occupational medicine. The other combined program is for internists subspecializing in pulmonary disease; it also leads to dual board eligibility. The first year is part of the regular clinical training program in pulmonary disease, and consists of a month as a primary physician in the Intermountain Respiratory Intensive Care Unit (IRICU) followed by five rotations of approximately ten weeks each in a pulmonary function laboratory, as supervisor of the IRICU, and as first consultant in each of the three university-affiliated hospitals. The second year is spent in the MSCM and the third year in research that emphasizes occupational lung disease.

The Pulmonary Disease Division has a close working relationship with the RMCOEH because many respiratory disorders may have occupational or environmental origins. The occupational lung disease course is taught by faculty of the division. Faculty in the Center may have appointments in Pulmonary Disease, and carry out research in occupational lung disease with faculty, staff and equipment of the pulmonary division. Consultation on inpatients with occupational lung disease is provided by Center faculty, and outpatient

TABLE 2.—*Outline of the Two Combined Programs Available in Association With the Rocky Mountain Center*

	Occupational Medicine	*Occupational and Family Medicine*	*Occupational and Pulmonary Medicine*
PGY 1	Clinical Training Family Practice	Clinical Training Family Practice	Clinical Training Internal Medicine
PGY 2	MSCM—Occupational and Environmental Health	Family Practice	Internal Medicine
PGY 3	Occupational Medicine 2nd year—Research, Clinical, Practical	Family Practice: 3 months; MSCM-Occupational and Environmental Health: 6 months; Family Practice: 3 months	Internal Medicine
	Board Eligible: Occupational Medicine		Board Eligible: Internal Medicine
PGY 4		Occupational Medicine 2nd year: Research, Clinical, Practical Board Eligible: Occupational Medicine and Family Practice	Clinical Pulmonary Rotations
PGY 5			MSCM-Occupational and Environmental Health
PGY 6			Occupational Medicine 2nd year: Research, Clinical, Practical Board Eligible: Occupational Medicine and Pulmonary Disease

MSCM = Master of Science in Community Medicine; PGY = postgraduate year

TABLE 3.—*MSCM: Industrial Hygiene and Safety Track*

Required	
Fundamentals of Industrial Hygiene	3.0
Advanced Topics in Industrial Hygiene	3.0
Industrial and Mining Safety	3.0
Industrial Toxicology	2.0
Interdisciplinary Seminar in Occupational Safety and Health	1.5
	12.5
Electives	
Noise Evaluation and Control*	3
Industrial Hygiene Chemistry*	3
Ventilation Engineering*	3
Field Experience in Occupational Safety and Health*	3
Readings in Environmental Health	2
Air Pollution Control Techniques	4
Radiation Biology	3
Law and Medicine	2
Statistical Methods in Epidemiology	3

MSCM = Master of Science in Community Medicine

*Recommended

evaluations for Workers' Compensation (such as the Federal Black Lung Program) are done cooperatively.

The teaching of these medical students provides an additional focus. Occupational medicine is taught to the first year students as an integral portion of "Disease and Society," through the Department of Family and Community Medicine. Environmental and occupational lung disease is taught as part of the pulmonary organ system to second year students. Occupational history taking is emphasized during the third-year internal medicine rotations. A four- to eight-week elective is provided for senior medical students to participate in research projects, serve a subinternship with the OCAW union or work in the Health Hazard Evaluations program.

Career opportunities are legion with the government (such as NIOSH, OSHA, State Health Departments, Environmental Protection Agency), industry, organized labor, consulting firms, group medical practices and academia.

MSCM: Industrial Hygiene and Safety

A graduate student with an engineering or science background may follow the MSCM's industrial hygiene and safety track (see Table 3). Industrial hygiene chemistry, ventilation engineering, and noise evaluation and control are strongly recommended. Field experience and a Master's thesis are required of each student. Employment opportunities for a graduate with a Master's degree in industrial hygiene are available in NIOSH (estimates a 4,000 person shortage nationally), OSHA, state and local government, industry, labor and private consulting groups.

MSCM: Occupational and Environmental Health

A graduate student admitted to the MSCM degree program may elect to concentrate in the occupational-environmental health track. Industrial toxicology (2 credits) is substituted for biochemical toxicology. The MSCM degree with this specialization is particularly useful for local health officers or environmental health specialists in small colleges, industry, local health departments or labor.

Occupational Health Nursing

A Master of Science and Practitioner Certificate in Occupational Health Nursing are offered by the College of Nursing. The graduate curriculum includes course work in general nursing, occupational health nursing and care, research and electives. The Master's program is completed in 18 months to two years, and the practitioner program (part-time) is nine months. Didactic training and practical field experience are emphasized. An occupational health nursing component to the baccalaureate curriculum is taught. Occupational health nurses provide a key function in industries in pre-employment examinations and health screening and monitoring.

Safety

As part of the RMCOEH, Utah State University (USU) in Logan, Utah, offers two Bachelor of Science programs: occupational safety and health, and public health (industrial hygiene option). The generalist program in occupational safety and health has been the most popular, with a safety component from the College of Engineering and a health component from the College of Science. Environmental and industrial toxicology is taught in all programs, and graduate (MS and PhD) training and research toxicology programs at USU complement the Center. The USU component involves participation in seminars and courses with the University of Utah Health Sciences Center, and credit transfers are easily arranged.

A Master of Science in Industrial Engineering

with a Safety Emphasis also has been developed at the University of Utah by RMCOEH.

Cross-Training

The interdisciplinary occupational safety and health seminar provides an opportunity for specialists in all four areas to analyze occupational health issues. Ordinarily, a guest speaker is invited to discuss an occupational health and safety problem (for example, the Regional OSHA Administrator to discuss the investigation of a lead smelter and subsequent legal challenge, or an attorney to discuss the rights of a pregnant worker). The occupational health nursing program as well as the industrial hygiene and occupational medicine programs have many courses in the core and specialty tracks in common. Students also participate in epidemiologic field surveys together to further eliminate barriers that may exist between physicians, nurses and engineers. The interdisciplinary seminar in occupational safety and health provides the opportunity to explore and learn how the team concept functions in occupational safety and health. Approximately 25 students can be accommodated in each of the University of Utah and Utah State University components of the Center's programs.

Continuing Education

Continuing education for occupational safety and health professionals is an essential function of the RMCOEH. A director for continuing education supervises the program. The Park City Environmental Health Conference is the major theme and academic conference held in March each year at Park City Ski Resort. The conference in 1979 was cosponsored by the Society for Occupational and Environmental Health, and entitled, "Health Implications of New Energy Technologies." The conference attracted international attention, and the proceedings were published. Nuclear, coal, oil shale, geothermal, solar, coal conversion technologies and energy transmission were discussed. The 1980 Park City Environmental Health Conference was entitled "Health and Exposures in the Smelter Environment," and was cosponsored by the Occupational Health Program of the Harvard School of Public Health.

Other major conferences include: (1) "Occupational Medicine for the Practicing Physician" in the fall (this conference alternates between Salt Lake City and Denver), (2) the Rocky Mountain Occupational Safety and Health Conference held annually in the region, (3) the annual Utah Industrial Hygiene Conference in September at Snowbird, Utah and (4) an annual Conference for Occupational Health Nursing in the fall in Salt Lake City. NIOSH courses such as Occupational Respiratory Protection and Occupational Health Nursing—Basic Theory and Update, are taught annually. Courses in industrial hygiene, ventilation, safety, industrial hygiene chemistry and a board review course are planned or sponsored each year.

Research

Research interests of the RMCOEH faculty and students cover the vast spectrum of occupational safety and health, but emphasis is placed on energy and mining-related problems. Examples of research include: cancer epidemiology using data from the Utah Cancer Registry (such as lung and other cancer incidence associated with exposure to smelter effluents or asbestos); immunologic impairments associated with effects of industrial exposures; effects on the reproductive system from occupational exposure; characterization of mineral fibers using electron microscopic techniques, and epidemiologic field surveys of a variety of workplace health problems (such as health status of underground coal miners and oil shale workers). In addition, occupational lung diseases (such as silicosis and allergic alveolitis) are major interests of several faculty members. Evaluation and control of occupational exposures, particularly of mine environments, are of special interest to the industrial hygiene faculty.

Administration

The Center concept for occupational safety and health has evolved because the field is multidisciplinary, yet is in need of an academic base. Because few, if any, medical schools have departments in occupational and environmental health, most centers have their academic base in preventive and community medicine departments or schools of public health. RMCOEH has its academic base primarily in a Division of Occupational and Environmental Health in the Department of Family and Community Medicine (DFCM).

The Director of RMCOEH reports directly to the Vice President for Health Sciences, similar to the Deans of the Colleges of Medicine, Nursing,

Pharmacy and Health. The nursing programs, the programs affiliated with USU, and continuing education programs are all coordinated by the RMCOEH Director. Supervision of the occupational medicine residency, industrial hygiene and safety program, and research areas is shared by the Director of RMCOEH and the Chief of the Division of Occupational and Environmental Health in DFCM. Currently, the RMCOEH Director and Division Chief are the same person. The Chief of the Division is responsible for RMCOEH faculty appointments in DFCM in the College of Medicine. An administrator reports directly to the Director of RMCOEH, and assists in planning budgets, preparing grants and contracts, fund-raising and solving the day-to-day operational problems.

Research grants and contracts are submitted through the Division of Occupational and Environmental Health or the Pulmonary Disease Division, and the appropriate departmental and college channels.

The RMCOEH is housed on one floor of a building adjacent to the University of Utah Health Sciences Center, and plans are being developed for additional research space. There are 25 full- or part-time faculty in the Center, and another 25 faculty participate to a lesser extent in the teaching and research programs.

Corticosteroids and Chronic Active Hepatitis

THERE ARE A LOT of questions now about the use of corticosteroids for treating chronic active hepatitis, and one more or less typifies them: Why use prednisolone instead of prednisone?

Well, the biochemical reason initially put forth was that prednisone must be acted on by the liver to produce prednisolone. Prednisone alone is not active; prednisolone is the active compound. It was thought, due to a series of studies done mainly by Dr. Powell (now in Australia) that this might make a difference —that is, in patients with very severe liver disease conversion of prednisone to prednisolone might be incomplete, thereby giving them a lower dose of active steroid during the acute phase of the illness. And if, for any reason, their condition began to get better later, then the conversion might be improved, thereby increasing their own effective dose. These changes with prednisolone are minor, however.

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Information

Office Diagnosis of Epididymitis, Epididymo-orchitis and Orchitis

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PAINFUL SCROTAL LESIONS constitute a small proportion of emergency presentations of urologic complaints, being eclipsed by ureteral colic and urinary tract infection. For this reason, these lesions are poorly diagnosed and frequently managed in a rather confused fashion. The recognized reticence of many junior medical students to "handle the scrotum" when learning the fundamentals of physical examination is retained to a minor degree by many physicians. This reticence often results in further obscuring an accurate diagnosis, because a clear knowledge of normal anatomy is lacking. It seems appropriate, therefore, to begin with a brief discussion of the normal findings on examination of the scrotal contents. These findings are reproducible and easily elicited, and form a basis for establishing the abnormal findings that may be present during acute inflammatory disease.

Anatomy

The scrotal contents and their relative positions can be most accurately and easily identified with the patient standing, facing the seated examiner. Consistency in this regard aids accuracy of diagnosis by fixing the *normal* in the examiner's mind.

The various layers of the abdominal wall contribute to the scrotal wall, and one of the most important of these is the cremasteric muscle—an extension of the internal oblique musculature. This muscle retracts the testes upwards as a protective mechanism during cold or sudden trauma. In the presence of inflammation or a substantial increase in testicular mass, such as may occur with tumors, this muscle loses its retractile capacity compared with the normal opposite side. Similarly, the dartos muscle (an extension of the fasciae of Camper and Scarpa) which causes the continuous involuntary contraction and relaxation of the scrotal skin is, in effect, paralyzed when there is pronounced inflammation of the scrotal contents. The scrotum assumes a reddened, glistening appearance, and the normal rugal folds are effaced.

The testes are elongated ovoids, with the long axis directed vertically. The epididymis characteristically is flattened along the long axis of the testes in a posterolateral orientation—on the side away from an examiner seated in front of the patient. One can normally distinguish clearly between the smooth testis and the somewhat irregular epididymis closely applied to it. The vas deferens lies on the posterior surface of the spermatic cord and is easily palpable as a firm cord-like structure about 3 mm in diameter. The softer cord structures containing the spermatic artery and its venous drainage, the pampiniform plexus, lie between the vertical vas and the examiner. An important exception to the posterior location of the vas deferens occurs when the epididymis lies on the anterior testicular surface, and in this instance the cord is, likewise, anterior. This fact is important to remember when searching for the vas while attempting to carry out a vasectomy. The appendix testis and appendix epididymis are not usually palpable, although readily identified on the exposed testicle during scrotal surgical procedures. Both structures are located on the upper portions of the testis and epididymis. These are müllerian and wolffian duct remnants, respectively. The epididymis is generally differentiated into a thickened upper portion (head or globus major) and a thinner, tapering lower portion that trails out to form the vas deferens (globus minor).

Epididymitis

Epididymitis is one of the painful lesions involving the scrotal contents. It rarely occurs in prepubertal males and, when it does, is almost always associated with a urinary tract infection. The usual case has no demonstrable urinary infec-

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tion, and the patient may not even be febrile. Its cause is unknown, but may relate to reflux of urine into the vas deferens during a Valsalva maneuver with subsequent chemical irritation, viral infection or other obscure phenomena. This explains the not infrequent history of onset of symptoms following strenuous activity such as lifting. It most often begins as a rather subtle complaint, a vague consciousness of the side of involvement. This progresses to discomfort and, finally, pain and moderate tenderness within 12 to 48 hours. The pain is rarely acute, but in some cases occurring on the right side there has been such severe guarding as to lead to an erroneous diagnosis of appendicitis. As the pain progresses, the epididymis becomes enlarged. Early cases may present as a precisely localized area of tenderness in one region of the epididymis, generally the globus major. Within hours, however, the epididymal swelling becomes more general. There may be an associated hydrocele, which while in the early stages may easily transilluminate. (All scrotal lesions should be transilluminated to differentiate solid lesions, such as testes tumors, from cystic masses such as hydroceles or spermatoceles.) Later, however, the fluid becomes turbid, and transillumination is less rewarding. In some cases, there is only epididymal involvement. More often than not, however, the testis becomes involved in the inflammation, and orchitis results. This compounds the morbidity and raises the specter of malignancy, because when the tenderness subsides, except for the history of inflammation, these lesions suggest large testicular tumors. They do not transilluminate, are massively enlarged, and the normal testicular/epididymal anatomy is temporarily obscured.

Treatment is empiric, with the usual approach being bedrest and cold compresses during the acute phase and warm sitz baths and a scrotal support during the convalescent phase. Broad spectrum antibiotic therapy is generally utilized, although rationale for it in the absence of documented infection is questionable. It has been suggested that acute epididymitis is usually associated with coliform or pseudomonas urinary tract infection in men over 35 years of age and with gonococcal or chlamydial urethritis in younger men.[1]

In the later stages, the striking size of the scrotal mass may confound even a physician who was secure initially in his diagnosis of epididymo-orchitis. It is crucial that the condition of convalescent patients be followed carefully over three to six months to make *sure* that the scrotal findings return to normal and that the testis returns to normal size over the ensuing period. At any time that the mass does not appear to be regressing or, even worse, appears to be increasing in size beyond the acute phase, immediate inguinal exploration of the offending lesion is mandatory to rule out the presence of a testicular tumor. A transscrotal approach is contraindicated in lesions where a tumor is suspected. In the finally resolved case, the testis will return completely to normal size, and the epididymis will retain an easily palpable area of thickening or scar which may never disappear.

Careful follow-up of patients with these lesions cannot be too strongly emphasized. Most experienced urologists have seen suspected cases of epididymo-orchitis that subsequently turned out to be testicular malignant lesions. Whether the tumor actually causes the epididymitis or whether the epididymo-orchitis obscures the initial development of the cancer in these perplexing cases is unknown. One worries most in treating patients who either did not consult a physician in the early stage of the epididymitis or, even worse, who did not see a physician until the pain had subsided. In these instances, one must take the patient's word that pain was present at the outset, and see him frequently until one is satisfied that the testis is normal. Any delay in resolution or atypical course should indicate surgical exploration.

Torsion of the Spermatic Cord

Included in the differential diagnosis of painful scrotal masses is torsion of the spermatic cord. This entity, usually referred to incorrectly as testicular torsion, frequently is misdiagnosed as epididymo-orchitis. This error is made in most city hospital emergency rooms five or six times each year and always results in the unnecessary loss of a testis. The two lesions, torsion and epididymitis, are similar only in that each one is painful. However, in every other aspect, they differ, and even the degree of pain in each is dissimilar. In torsion, the pain is sudden and acute. The patient is well one instant and doubled over the next. The pain is relatively short-lived, and if physician contact is delayed for even 24 hours, the pain generally has lessened. These patients are dramatically affected initially; they may cry out or even vomit with the severe pain. There are two peak age incidences; the first is in the newborn

period when the pain is completely overlooked. The second peak incidence occurs around the time of puberty and extends into the 20's. These older patients overlap with those who present with epididymo-orchitis, and these are the ones who are often misdiagnosed as having epididymitis. Given antibiotics and analgesics, they are reassured that the pain will go away. It always does, but the infarcted testicle later requires removal, and fertility has been placed at risk unnecessarily. Because torsion can and does occur subsequently in the contralateral testis, the possibility of total loss of testicular function arises.

Besides the acute nature of the pain, there are other useful differentiating characteristics. The testis in torsion is high-riding in the ipsilateral scrotum. The twisted spermatic cord becomes foreshortened, leading to the pathological retraction of the testis superiorly. The ipsilateral spermatic cord in torsion is normal. This can sometimes be palpated in the inguinal canal and then compared with the opposite side. If the cord diameters are similar, torsion is the most likely diagnosis. When epididymitis is present, the ipsilateral cord is not only indurated, but generally tender, and the ipsilateral seminal vesicle and hemiprostate may be similarly swollen on rectal examination. Most authors describe pyuria as a helpful finding in substantiating a diagnosis of epididymitis. Pyuria is absent in torsion of the spermatic cord. Similarly, in early torsion of the cord, the patient is usually afebrile, whereas in epididymitis a low-grade fever is often found.

Two additional diagnostic techniques which can be useful in the differentiation of epididymitis and torsion of the spermatic cord are the use of the Doppler instrument[2] and scrotal scanning.[3,4]

The Doppler instrument is a simple mechanism that measures blood flow past a point as pulsations interfere with a constant ultrasonic wave. The pulsations are then magnified to audible level. Torsion is associated with absence of blood flow to the affected testis, whereas increased flow is noted in epididymitis associated with inflammation and hyperemia. This technique is noninvasive, easily accessible, quick and quite useful in confirmation of clinical opinion.

Nuclear angiography is also useful in this clinical situation. This technique again measures presence or absence of blood flow to an affected testis and has been quite reliable, although it is not as readily available in an office as is the Doppler instrument. One sees a *cold spot* usually surrounded by a *halo* of increased activity in torsion of the spermatic cord as opposed to increased isotope concentration, or *hot spots,* in inflammatory conditions with an epididymitis/orchitis.

The implications of a mistaken diagnosis of epididymitis in a patient who actually suffers from torsion of the spermatic cord are so unfortunate that to err on the side of surgical differentiation in questionable presentation seems wise. Because the cause of pubertal torsion is a congenitally elongated epididymal mesentery, allowing easy rotation of the testis on the cord, contralateral surgical exploration must be carried out to fix the opposite testis in place. In the absence of pain, this situation can be easily ascertained, because the testis, instead of being in its normal vertical orientation, lies horizontally in the scrotum. This physical finding is helpful, not only in establishing a diagnosis in the presence of acute contralateral torsion, but in determining the cause of intermittent complaints of acute testicular pain in young boys who have spontaneously "detorsed" their testes by the time they reach their physician.

Torsion of an Appendage

Torsion of the appendix testis or appendix epididymis can occur in young boys also. Here,

TABLE 1.—*Differential Diagnosis of Painful Scrotal Lesions*

	Epididymitis	*Torsion of Spermatic Cord*
Age of onset	Generally greater than 15 years Extends into 20's and 30's	Perinatal peak; peripubertal peak Extends into 20's and 30's
Character of pain	Gradual in onset	Sudden, acute, severe
Position of testes	Dependent	Retracted; high-riding
Fever	Sometimes present, low-grade	Absent
Analysis of urine	± Pus cells	No pyuria
Ipsilateral spermatic cord	Thickened	Normal
Ipsilateral seminal vesicle	Boggy	Normal
Contralateral testis	Normal vertical orientation	Possible horizontal orientation

the pain is less acute, and initially the tenderness is confined to the upper pole of the testis. Sometimes in prepubertal males, the *blue-dot sign* can be diagnosed. In these cases, the infarcted appendix can be seen through the thinned scrotal skin. These lesions often have a prolonged morbidity with associated hydrocele formation, and we generally explore them surgically to remove the offending appendix. Exploration of the contralateral appendix is not indicated as it is in torsion of the spermatic cord.

The differential diagnosis of painful scrotal lesions is summarized in Table 1.

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Refer to: Borelli LN: Backache: Its changing prevalence (Information). West J Med 133:273-275, Sep 1980

Information

Backache: Its Changing Prevalence

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In 1974 California hospitals discharged 3,644,770 patients; in 1977 the number discharged was 2,758,122, representing a 24.3 percent decline over the three years.[1] This decline in hospital use remains unexplained, but the same phenomenon seems to have affected the rate of hospitalization for low back pain.

In 1977 Homer C. Pheasant[2] calculated the incidence and cost of inpatient care for low back pain in California. His findings were based on the *Length of Stay in California Hospitals (1974),*[3] an independent compendium of hospital discharges and surgical procedures which gives a fairly representative survey of hospital usage in California. This article compares the 1974 statistics with those of 1977.

There are 13 diagnostic categories that represent almost all conditions identified as backache. From the tables listed in *Length of Stay in California Hospitals,* it is possible to determine the average length of stay and the total number of patient days. This 1974 edition surveyed 214 hospitals with 33 percent of all hospital beds, and in 1977 it dealt with 205 hospitals and 36 percent of all hospital beds in the state. From the above information, the total projected number of hospital discharges and total patient days were calculated and compared (Table 1).

Nearly 23 percent fewer patients were in California hospitals in 1977 with complaints of low back pain than in 1974. This decline closely parallels the 24.3 percent decline in overall discharges. With the exception of three specific diagnostic categories: prolapse of the lumbosacral disc (decreased 25.7 percent), lumbalgia (decreased 8.4 percent), and strain and sprain of other unspecified parts of the back (decreased 3.2 percent), the largest declines in hospital usage were in the less specific diagnostic categories of back pain, such as prolapsed disc at unspecified sites (decreased 38.1 percent), strain or sprain of the lumbosacral joint (decreased 36.9 percent), lumbar strain or sprain (decreased 34.4 percent) and low back pain (decreased 24.8 percent). However, some specific diagnostic categories did not have a proportionate decline and, in fact, had a relative increase such as sciatica (decreased 6.0 percent) and radicular syndrome of the lower extremities (decreased 8.8 percent) when compared with the overall decline in hospital discharges of 24.3 percent.

From the length of stay data, the total number of patients who underwent surgical procedures for

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TABLE 1.—*Projected Total Hospital Discharges Classified by Diagnosis (ICDA)*

Diagnostic Descriptor (ICDA)	Number of Patients				Average Stay			Total Patient Days		
	1974	1977	Percent Change	Relative Change*	1974	1977	Percent Change	1974	1977	Percent Change
Prolapsed disc, lumbosacral	30,789	22,886	−25.7	− 1.4	10.3	9.8	− 4.9	317,127	224,284	−22.3
Sprain or strain of lumbosacral joint	13,995	8,833	−36.9	−12.6	7.4	6.8	− 8.1	103,563	60,067	−42.0
Lumbalgia	6,492	5,947	− 8.4	+15.9	7.3	7.3	0	47,392	43,415	− 8.4
Fracture and fracture dislocation of vertebral column without mention of spinal cord lesion	5,775	5,181	−10.3	+14.0	9.8	9.4	− 4.1	56,595	48,697	−14.0
Sprain or strain of other unspecified parts of back	5,439	5,261	− 3.2	+21.1	7.4	7.5	+ 1.4	40,249	39,458	− 2.0
Low back pain	3,192	2,400	−24.8	− 0.5	7.7	8.1	+ 5.4	24,578	19,440	−20.9
Radicular syndrome of lower extremities	2,310	2,106	− 8.8	+15.5	8.3	8.3	0	19,173	17,476	− 8.9
Prolapsed disc at unspecified sites	2,079	1,286	−38.1	−13.8	9.9	8.6	−13.1	20,578	11,299	−45.1
Sprain or strain, lumbar	1,377	903	−34.4	−10.1	7.0	6.1	−12.9	9,639	5,507	−42.9
Sciatica	1,199	1,125	− 6.0	+18.3	7.8	8.4	+ 7.7	9,337	9,450	+ 1.2
Lumbago	NL	1,397	..	..	NL	8.6	..	...	12,016	..
Prolapsed disc at a specified site	NL	92	..	..	NL	7.9	..	...	724	..
Disorders of sacroiliac	NL	467	..	..	NL	6.9	..	...	3,220	..
California total (excluding lumbago, prolapsed disc at specific site, and disorders of sacroiliac)	72,645	55,928	..	..	..	..	..	648,234	479,095	..
Average value	...	...	−23.0	+ 0.4	8.92	8.03	−10	...	...	−26.2

ICDA = International Classification of Diseases Adapted; NL = not listed

*Relative change figures computed in relation to average percentage change of −24.3.

TABLE 2.—*Hospital Discharges Classified by Procedure**

Diagnostic Descriptor	Number of Patients			Average Stay (Days)			Total Patient Days		
	1974	1977	Percent Change	1974	1977	Percent Change	1974	1977	Percent Change
Excision of intervertebral disc (prolapsed disc)	13,365	9,536	−28.6	14.2	13.4	−5.6	189,783	127,784	−32.7
Laminectomy	3,639	3,375	− 7.3	17.1	15.9	−7.0	62,227	53,663	−13.8
Spinal fusion	3,039	2,467	−18.8	15.8	16.1	+1.9	48,016	39,713	−17.3

*Sources: Health Data Corporation (1974),[1] Pheasant[2] and Health Data Corporation (1977).[3]

TABLE 3.—*Surgical Versus Medical Management**

	Number of Patients				Total Patient Days			
	1974	Percent	1977	Percent	1974	Percent	1977	Percent
Discharged from hospital	72,645	100	57,883	100	648,234	100	479,093	100
Surgical procedures	20,043	27.6	15,378	26.6	300,024	46.3	221,160	46.2
Medical treatment	52,602	72.4	42,505	73.4	348,210	53.7	257,933	53.8

*Sources: Health Data Corporation (1974),[1] Pheasant[2] and Health Data Corporation (1977).[3]

their back complaints was determined (Table 2). In 1977, 28.6 percent fewer patients were treated surgically with disc excisions, 7.3 percent fewer patients with laminectomies and 18.8 percent fewer patients with spinal fusion. Yet, the percentage of these patients treated surgically or medically had changed minimally (Table 3).

TABLE 4.—*California State Statistics**

	1974	*1977*
Population of California	20,907,000	21,827,000
Total California hospital discharges	3,280,293	2,758,122
California low back pain discharges	72,645	55,928
California hospital discharges for low back pain per 100,000 population	347.47	256.23
Percentage of hospital discharges for low back pain	2.21	2.03
Laminectomies	3,639	3,375
Discectomies	13,365	9,536
Total surgical procedures	17,004	12,911
Surgical procedures for low back pain per 1,000 hospital discharges	5.18	4.68

*Sources: Health Data Corporation (1974),[1] Pheasant[2] and Health Data Corporation (1977).[3]

When the total number of California hospital discharges for low back pain (Table 4) and the total number of operative procedures for low back pain, and the total number of hospital discharges for the state for the years 1974 and 1977 are related to the population of California,[4] it can be determined that 2.21 percent of the hospital discharges in 1974 were for low back pain compared with 2.03 percent in 1977; that 347 people per 100,000 population were discharged for low back pain in 1974 compared with 256 in 1977; and that 5.18 operative procedures per 1,000 hospital patients were done in 1974 compared with 4.68 in 1977. Of all the above findings, the most dramatic is the 26.1 percent decline in total patient days for low back pain during a period when the population of the state rose.

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ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

Use of the Progestogen Challenge Test to Reduce the Risk of Endometrial Cancer

Gambrell RD, Jr, Masses FM, Castaneda TA, et al
Obstetrics & Gynecology
55:732-738, Jun 1980
DISCIPLINES: Obstetrics and Gynecology, Surgery
READABILITY: Very good

These authors found that the incidence of endometrial cavity in postmenopausal women treated with cyclic estrogen-progestogen was significantly lower than in untreated women or in women given unopposed estrogen.

Association of Induced Abortion With Subsequent Pregnancy Loss

Levin AA, Schoenbaum SC, Monson RR, et al
JAMA
243:2495-2499, Jun 27, 1980
DISCIPLINES: Family Practice, Obstetrics, Gynecology, Surgery
READABILITY: Excellent

In reviewing the case load of the Boston Hospital for Women between 1976 and 1978 the authors concluded that two or more induced abortions result in a twofold to threefold increase in the risk of first trimester spontaneous abortion in subsequent pregnancies. Conclusion: abortion cannot be considered a valid means of "backup" contraceptive.

Abruptio Placentae and Placenta Previa: Frequency, Perinatal Mortality, and Cigarette Smoking

Naeye RL
Obstetrics & Gynecology
55:701-704, June 1980
DISCIPLINES: Obstetrics, Family Practice
READABILITY: Very good

Pregnant women should not smoke. In this prospective study the author concluded that there is a causal relationship between cigarette smoking and the fetal and neonatal deaths resulting from abruptio placentae and placenta previa, with the highest incidence in women over 30.

Diagnosis of Intra-abdominal and Pelvic Abscesses by Computerized Tomography

Koehler PR, Moss AA
JAMA
244:49-52, Jul 4, 1980
DISCIPLINES: Obstetrics, Gynecology, General Surgery, General Practice
READABILITY: Very Good

Pelvic abscess, unlike other pelvic masses, can elude accurate diagnosis by the usual clinical examination. Moreover, improper diagnosis or inadequate treatment can prove fatal. These authors, working at the University of Utah and the University of California, San Francisco, conclude the "CT is an accurate, fast, and cost-effective examination for the diagnosis of [pelvic] abscesses."

Ultrasonographic Versus Clinical Evaluation of a Pelvic Mass

Reeves RD, Drake TS, O'Brien WF
Obstetrics & Gynecology
55:551-554, May 1980
DISCIPLINES: Family Practice, Obstetrics, Gynecology, Surgery
READABILITY: Very good

There was no significant difference in the accuracy of pelvic ultrasonographic examinations as compared with clinical examinations in detection, estimation of size or determination of the position of the mass. Unless the cystic or solid nature of the mass will modify the patient's treatment there is no need for routine preoporative ultrasonographic evaluation.

—E. R. W. FOX, MD
Coeur d'Alene, ID

* * *

Postoperative Chest Radiograph: I. Alterations After Abdominal Surgery; II. Alterations After Major Intrathoracic Surgery

Goodman LR
American Journal of Roentgenology
134:533-541, 803-813, Mar, Apr 1980
DISCIPLINES: Radiology, Chest Disease, Thoracic Surgery, Abdominal Surgery
READABILITY: Very good

An excellent review of the use of radiography of the chest following major abdominal or intrathoracic operations. By careful attention to timing and clinical setting, the author distinguishes between those radiographic findings that are to be expected following surgical operation and those representing complications of significant clinical importance.

—MARSHALL ROWEN, MD
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Endorphins—Morphine-like Peptides of Brain

Cleghorn RA
Canadian Journal of Psychiatry
25:182-186, Mar 1980
DISCIPLINES: Endocrinology, Psychobiology
READABILITY: Very good

In the form of a commentary the author gives a most lucid, short historical review of the discovery and development of both endorphins and enkephalins. In a few short paragraphs the new substances are related to the catecholamine theory of mental disorders. The review refers to significant foreign research and demonstration of clinical experiments. Citing one of these the author says, "symptoms observed in schizophrenia may result from a disturbance in the balance of Alpha and Y-type endorphins." The final sentence is intriguing for its understatement, "this hypothesis places psychopathology in the orbit of endocrine or metabolic disease susceptible to amendment in the same way as diabetes or myxedema."

—J. M. STUBBLEBINE, MD
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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

THE HOSPICE STORY IN CALIFORNIA—Third Edition—California Medical Association, Committee on Evolving Trends in Society Affecting Life. Sutter Publications, Inc., 731 Market Street, San Francisco, CA (94103), 1979. 215 pages, $10.00.

The July 1978 issue of THE WESTERN JOURNAL OF MEDICINE contained an article providing information on the status of the hospice movement in the state of California as of the early part of that year ("Hospices for Terminally Ill Patients"). The article dealt with the hospice concept, the recommendations of the California Medical Association's (CMA) Committee on Evolving Trends in Society Affecting Life, and the action of the CMA in support of that concept. The main body of the article discussed the results of a survey conducted in February 1978 to determine the characteristics of California hospices, as well as some preliminary information on costs. The overview mentioned some then-existing problems and raised a question about one of the observed weaknesses of the movement in that it did not always show evidence of having a broad cross-section of community support. The following months witnessed a tremendous surge of activity in communities throughout California to initiate planning and organizational efforts to respond to the interest shown by the public and health professionals in hospice development. The Committee on Evolving Trends in Society Affecting Life authorized the collection of more current data and the publication of another edition of *The Hospice Story in California,* a compilation which had gone through two editions and which contained descriptions of the history, structure, organization, and operation of 12 and 13 hospices, respectively, which had submitted reports based on an outline previously provided to them.

From the 16 hospices known to be operational in the early part of 1978, the number had grown to approximately 40 in the spring of 1979; at least a dozen others were on the verge of starting their programs. Questions addressed to the Committee by other physicians, state and county medical associations, community groups, and health and social work professionals prompted the request to the hospices to update their material as well as to provide demographic data about their patients and to include examples of evaluation efforts which could be utilized by other hospices.

The third edition of *The Hospice Story in California* contains information submitted by the hospices describing the beginning efforts at data collection and provides information about the characteristics of terminally ill patients, duration of hospice services, costs of providing such services, budgets, sources of funding and some of the problems encountered. Included are many references to future plans, indicating what problems have yet to be overcome.

The publication contains descriptions of 41 hospices, three of which are not yet operational but whose experiences were considered worth sharing with other groups in their developmental stages.

Analysis of the data pertaining to the programs in operation as of July 1 shows that more than half of them (21) started during 1978-79; almost as many were begun in 1978 as had started during the previous four years.

The 38 hospices are located in 22 of the 58 counties in California, with some drawing patients from more than the county in which they are situated. As might be expected, Los Angeles County has the greatest number, while Ventura, San Diego, Santa Barbara, Sonoma, and Contra Costa each have more than one.

Among the sources of hospice sponsorship, broad-based community support ranks first; half of the hospices fall in this category, followed closely by hospital sponsorship. In the latter, the hospital board of directors generally serves as the hospice board, although a question may be raised as to the nature and extent of their interest and involvement inasmuch as their first allegiance is to the hospital itself.

Oriented as hospices are to home care services, it is not surprising to find that the majority of the hospices have the homes of terminally ill patients as the primary sites of service. Hospices also provide their services to patients when they are confined to a hospital, nursing or convalescent facility at some time during the course of illness. In those hospices that are hospital-based, home care services are provided to supplement in-patient services.

The necessity of having a medical director either part or full time, or on a consulting basis, is readily recognized by virtually all of the hospices. The medical director serves as an important link in the continuing relationship with the patient's physician and provides the professional direction/supervision that is a necessary part of the interdisciplinary team in which nurses, other health professionals, clergy and volunteers play an important role.

Medical or professional advisory committees (or both) are evident in more than half of the hospice programs.

The importance of adequate training of all personnel, whether paid or volunteer, is acknowledged by all hospices, as is the emphasis on the importance of identifying the hospice concept with an interdisciplinary effort, without which no hospice can succeed.

The importance of broadening the base of community support and representation is being recognized, as is the need for more uniform data collection and evaluation. It would appear that at present most of the evaluation measures take the form of internal discussions among staff regarding patient response to care and physician acceptance of the program. A handful of hospices have gone beyond this stage of evaluation and are employing more sophisticated measures and techniques. It is expected that evaluation efforts of all the hospices will expand in this direction as they gain more experience and become more firmly established.

The latest edition of *The Hospice Story in California* calls attention to one serious deficiency. Descriptions of hospice activity and services rarely mention that terminally ill patients will be served *regardless of their ability to pay*. This omission appears to negate a basic element and principle of the philosophy of hospice care, one which has survived over the centuries and is again emerging as a potent force—that of demonstrating the qualities of humanity and compassion which bind all people.

MURRAY KLUTCH
Director of Research
California Medical Education and Research Foundation
San Francisco

in memoriam

California Medical Association

Baker, Frances, Burlingame. Died April 20, 1979 in Burlingame, aged 84. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr. Baker was a retired member of the San Mateo County Medical Society.

Bennett, Dudley W., San Francisco. Died August 2, 1980, aged 81. Graduate of the University of California Medical School, Berkeley-San Francisco, 1926. Licensed in California in 1926. Dr. Bennett was a retired member of the San Francisco Medical Society.

Cook, Wells C., Los Angeles. Died May 18, 1979, aged 76. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Dr. Cook was a member of the Los Angeles County Medical Association.

Hosmer, Matthew N., San Francisco. Died August 6, 1980 in Greenbrae, aged 84. Graduate of the University of California Medical School, Berkeley-San Francisco, 1924. Licensed in California in 1924. Dr. Hosmer was a retired member of the San Francisco Medical Society.

Kleeman, George E., Oakland. Died July 13, 1980 in Oakland, aged 72. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr. Kleeman was a member of the Alameda-Contra Costa Medical Association.

Knox, John F., Glendale. Died June 25, 1980 in Glendale of complications following hip fracture surgical operation, aged 65. Graduate of the University of Nebraska College of Medicine, Omaha, 1940. Licensed in California in 1942. Dr. Knox was a member of the Los Angeles County Medical Association.

Konttas, Pearl V., Santa Rosa. Died July 12, 1980 in Santa Rosa, aged 86. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1923. Licensed in California in 1926. Dr. Konttas was a retired member of the Sonoma County Medical Association.

Merrill, John A., Monterey. Died September 24, 1979 in Carmel of pneumonia, aged 81. Graduate of the University of California Medical School, Berkeley-San Francisco, 1926. Licensed in California in 1926. Dr. Merrill was a retired member of the Monterey County Medical Society.

Rooney, John G., Santa Monica. Died June 26, 1980, aged 69. Graduate of the Creighton University School of Medicine, Omaha, 1935. Licensed in California in 1936. Dr. Rooney was a retired member of the Los Angeles County Medical Association.

Tanaka, Roy Kiyoshi, San Diego. Died July 14, 1980 in San Diego, aged 73. Graduate of the University of Minnesota Medical School, Minneapolis, 1936. Licensed in California in 1936. Dr. Tanaka was a member of the San Diego County Medical Society.

Teton, Joseph B., Santa Clara. Died August 3, 1980 in San Francisco, aged 70. Graduate of the University of Illinois College of Medicine, Chicago, 1934. Licensed in California in 1972. Dr. Teton was a member of the Santa Clara County Medical Society.

Virtue, Clark W., La Mesa. Died July 10, 1980, aged 77. Graduate of the University of Cincinnati College of Medicine, 1928. Licensed in California in 1956. Dr. Virtue was a retired member of the San Diego County Medical Society.

Wesely, Howard D., Modesto. Died October 28, 1979 of heart disease, aged 49. Graduate of the University of Nebraska College of Medicine, Omaha, 1956. Licensed in California in 1960. Dr. Wesely was a member of the Stanislaus Medical Society.

Wiseley, Dean V., Covina. Died June 30, 1980 of heart disease, aged 56. Graduate of the University of Southern California School of Medicine, Los Angeles, 1954. Licensed in California in 1954. Dr. Wiseley was a member of the Los Angeles County Medical Association.

Utah State Medical Association

Gorishek, William Martin, Price. Died July 11, 1980 in Price, aged 66. Graduate of Louisiana State University School of Medicine, New Orleans, 1940. Licensed in Utah in 1940. Dr. Gorishek was a member of the Carbon County Medical Society.

Sanders, Myrle Sharp, Salt Lake City. Died July 12, 1980 in Salt Lake City, aged 80. Graduate of St. Louis University School of Medicine, 1940. Licensed in Utah in 1941. Dr. Sanders was a member of the Salt Lake County Medical Society.

Weggeland, Thomas Courtney, Salt Lake City. Died July 15, 1980 in Salt Lake City, aged 80. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1928. Licensed in Utah in 1931. Dr. Weggeland was a member of the Salt Lake County Medical Society.

Washington State Medical Association

Luth, Duncan V., Spokane. Died July 19, 1980, aged 65. Graduate of the University of Minnesota Medical School, Minneapolis, 1942. Licensed in Washington in 1954. Dr. Luth was a member of the Spokane County Medical Society.

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CALIFORNIA MEDICAL ASSOCIATION ACCREDITED CONTINUING MEDICAL EDUCATION

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances, anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months

Precautions: In depression accompanying anxiety, consider possibility for suicide

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions

Observe usual precautions with impaired renal or hepatic function

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease

Safety and effectiveness in children under 12 years have not been established

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia, some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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Why one benzodiazepine and not another?

Are you concerned about long-acting metabolites? Many clinicians, as well as pharmacologists, are beginning to draw attention to this problem (see New England Journal of Medicine, April 5, 1979).

In contrast to some older benzodiazepines, Ativan (lorazepam) does not give rise to long-lasting active metabolites. As with all benzodiazepines, you should follow the usual precautions concerning co-administration with other CNS depressants and warn your patients against operating dangerous machinery and motor vehicles.

However, it is noteworthy that Ativan showed no clinical evidence of accumulation even when given in high doses over periods up to 6 months. The half-life of free lorazepam is about 12 hours; steady-state serum levels are attained in 2-3 days. Comparable data for diazepam: 20-50 hours and at least 7-10 days. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Ativan has a convenient b.i.d. or t.i.d. dosage schedule; it is compatible with a long list of other medications and, of course, it is a highly effective anxiolytic agent, as established in numerous nationwide, double-blind, controlled evaluations in thousands of patients.

See important information on preceding page.

Ativan® (IV) for (lorazepam) Anxiety

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Roche announces

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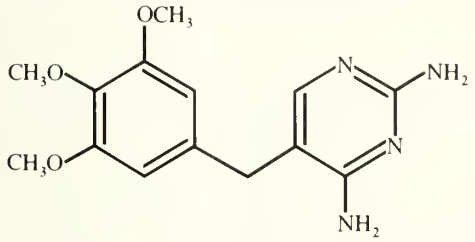
trimethoprim/ROCHE

Please see following page for complete product information.

Trimpex® 100-mg scored tablets

trimethoprim/ROCHE

DESCRIPTION: Trimpex (trimethoprim/Roche) is a synthetic antibacterial, available in scored white tablets, each containing 100 mg trimethoprim. Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.3 and the following structural formula:



CLINICAL PHARMACOLOGY: Trimethoprim is rapidly absorbed following oral administration. Mean peak serum levels of approximately 1.0 mcg/ml occur 1 to 4 hours after oral administration of a single 100 mg dose. The half-life of trimethoprim is 8 to 10 hours. Trimethoprim exists in the blood as free, protein-bound and metabolized forms. Approximately 44% of trimethoprim is protein-bound in the blood. The free form is considered to be the therapeutically active form.

Excretion of trimethoprim is chiefly by the kidneys through glomerular filtration and tubular secretion. Urine concentrations of trimethoprim are considerably higher than are the concentrations in the blood. Trimethoprim urine levels, after a single oral dose of 100 mg, ranged from 30 to 160 mcg/ml during the 0 to 4 hour period and declined to approximately 18 to 91 mcg/ml during the 8 to 24 hour period.

After oral administration, 50% to 60% of trimethoprim is excreted in the urine within 24 hours, approximately 80% of this being unmetabolized trimethoprim.

Microbiology: Trimpex blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. Thus, Trimpex selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of Trimpex includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*.

Representative Minimum Inhibitory Concentrations
For Trimethoprim-Susceptible Organisms

Bacteria	Trimethoprim MIC—mcg/ml (Range)
Escherichia coli	0.05—1.5
Proteus mirabilis	0.5—1.5
Klebsiella pneumoniae	0.5—5.0
Enterobacter species	0.5—5.0

The recommended quantitative disc susceptibility method[1,2] may be used for estimating the susceptibility of bacteria to Trimpex (trimethoprim/Roche). Reports from the laboratory giving results of the standardized test using the 5 mcg trimethoprim disc should be interpreted according to the following criteria:

Organisms producing zones of 16 mm or greater are classified as susceptible whereas those producing zones of 11 to 15 mm are classified as having intermediate susceptibility. A report from the laboratory of "Susceptible to trimethoprim" or "Intermediate susceptibility to trimethoprim" indicates that the infection is likely to respond when, as in uncomplicated urinary tract infections, effective therapy is dependent upon the urine concentration of trimethoprim.

Organisms producing zones of 10 mm or less are reported as resistant, indicating that other therapy should be selected.

Dilution methods for determining susceptibility are also used, and results are reported as the minimum drug concentration inhibiting microbial growth (MIC).[3]

If the MIC is 8 mcg per ml or less, the microorganism is considered "susceptible." If the MIC is 16 mcg per ml or greater, the microorganism is considered "resistant."

Normal vaginal and fecal flora are the source of most pathogens causing urinary tract infections. It is therefore relevant to consider the suppressive effect of trimethoprim in these sites.

Concentrations of trimethoprim in vaginal secretions are consistently greater than those found simultaneously in the serum, being typically 1.6 times the concentration of simultaneously obtained serum samples. Sufficient trimethoprim is excreted in the feces to markedly reduce or eliminate trimethoprim-susceptible organisms from the fecal flora.

The dominant fecal organisms (non-*Enterobacteriaceae*), *Bacteroides* spp. and *Lactobacillus* spp., are not susceptible to trimethoprim levels obtained with the recommended dosage.

INDICATIONS AND USAGE: For the treatment of initial episodes of uncomplicated urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae* and *Enterobacter* species.

Cultures and susceptibility tests should be performed to determine the susceptibility of the bacteria to trimethoprim. Therapy may be initiated prior to obtaining the results of these tests.

CONTRAINDICATIONS: Trimpex (trimethoprim/Roche) is contraindicated in individuals hypersensitive to trimethoprim and in those with documented megaloblastic anemia due to folate deficiency.

WARNINGS: Experience with trimethoprim alone is limited, but it has been reported rarely to interfere with hematopoiesis, especially when administered in large doses and/or for prolonged periods.

The presence of clinical signs such as sore throat, fever, pallor or purpura may be early indications of serious blood disorders. Complete blood count should be obtained if any of these signs are noted in a patient receiving trimethoprim and the drug discontinued if a significant reduction in the count of any formed blood element is found.

PRECAUTIONS: *General:* Trimethoprim should be given with caution to patients with possible folate deficiency. Folates may be administered concomitantly without interfering with the antibacterial action of trimethoprim. Trimethoprim should also be given with caution to patients with impaired renal or hepatic function.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Trimethoprim has been shown to be teratogenic in the rat when given in doses 40 times the human dose. In some rabbit studies, the overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses 6 times the human therapeutic dose. While there are no large well-controlled studies on the use of trimethoprim in pregnant women, Brumfitt and Pursell[4] reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim plus sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received trimethoprim plus sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim may interfere with folic acid metabolism, Trimpex should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Trimethoprim is excreted in human milk. Because trimethoprim may interfere with folic acid metabolism, caution should be exercised when Trimpex is administered to a nursing woman.

Pediatric Use: Safety of trimethoprim in infants under two months of age has not been demonstrated. The effectiveness of trimethoprim has not been established in children under 12 years of age.

ADVERSE REACTIONS: The adverse effects encountered most often with trimethoprim were rash and pruritus. Other adverse effects reported involved the gastrointestinal and hematopoietic systems.

Dermatologic Reactions: Rash, pruritus and exfoliative dermatitis. At the recommended dose of 100 mg b.i.d., the incidence of rash is 2.9%. In clinical studies which employed high doses of Trimpex, an elevated incidence of rash was noted. These rashes were maculopapular, morbilliform, pruritic and generally mild to moderate, appearing 7 to 14 days after the initiation of therapy.

Gastrointestinal Reactions: Epigastric distress, nausea, vomiting and glossitis.

Hematologic Reactions: Thrombocytopenia, leukopenia, neutropenia, megaloblastic anemia and methemoglobinemia.

Miscellaneous Reactions: Fever, elevation of serum transaminase and bilirubin, and increases in BUN and serum creatinine levels.

OVERDOSAGE: *Acute:* Signs of acute overdosage with trimethoprim may appear following ingestion of 1 gram or more of the drug and include nausea, vomiting, dizziness, headaches, mental depression, confusion and bone marrow depression (see CHRONIC OVERDOSAGE). Treatment consists of gastric lavage and general supportive measures. Acidification of the urine will increase renal elimination of trimethoprim. Peritoneal dialysis is not effective and hemodialysis only moderately effective in eliminating the drug.

Chronic: Use of trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. If signs of bone marrow depression occur, trimethoprim should be discontinued and the patient should be given leucovorin, 3 to 6 mg intramuscularly daily for three days, or as required to restore normal hematopoiesis.

DOSAGE AND ADMINISTRATION: The usual oral adult dosage is 100 mg of Trimpex (trimethoprim/Roche) every 12 hours for 10 days.

The use of trimethoprim in patients with a creatinine clearance of less than 15 ml/min is not recommended. For patients with a creatinine clearance of 15 to 30 ml/min, the dose should be 50 mg every 12 hours.

The effectiveness of trimethoprim has not been established in children under 12 years of age.

HOW SUPPLIED: Tablets, containing 100 mg trimethoprim—bottles of 100; Tel-E-Dose® packages of 100; and Prescription Paks of 20.

REFERENCES:

1. Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic susceptibility testing by standardized single disc method, *Am J Clin Pathol 45*:493-496, 1966
2. Approved Standard ASM-2 Performance Standards for Antimicrobial Disc Susceptibility Test. National Committee for Clinical Laboratory Standards, 771 East Lancaster Avenue, Villanova, Pennsylvania 19085
3. Ericsson HM, Sherris JC: Antibiotic sensitivity testing. Report of an international collaborative study, *Acta Pathol Microbiol Scand*, Section B, Suppl. 217, 1971, pp. 1-90
4. Brumfitt W, Pursell R: Trimethoprim/sulfamethoxazole in the treatment of bacteriuria in women, *J Infect Dis 128* (Suppl): S657-S663, 1973

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UTAH STATE MEDICAL ASSOCIATION

USMA 85th Annual Meeting

October 1 through October October 3, 1980 • Hotel Utah, Salt Lake City

WEDNESDAY, OCTOBER 1

Course No. 1

INFLAMMATORY BOWEL DISEASE

GILBERT L. WRIGHT, MD, and
J. KENT NELSON, MD, Co-Moderators

2:00 pm

INTRODUCTION

GILBERT L. WRIGHT, MD, and
J. KENT NELSON, MD

I. Diverticular Disease

2:10 pm

PATHOGENESIS, Workup and Medical Treatment

EDWIN ENGLERT, Jr, MD
Professor of Medicine
University of Utah College of Medicine
Salt Lake City, Utah

2:25 pm

INDICATIONS AND TYPES OF SURGERY FOR DIVERTICULAR DISEASE

RUPERT B. TURNBULL, Jr, MD
Department of Colon and Rectal Surgery
Santa Barbara Medical Foundation Clinic
Santa Barbara, California

II. Crohn's Disease and Chronic Ulcerative Colitis

2:55 pm

SIMILARITIES AND DIFFERENCES IN CLINICAL COURSE, COMPLICATIONS, GASTROENTEROLOGIC WORKUP AND MEDICAL TREATMENT

G. KENNETH JOHNSON, MD
Ogden, Utah

3:10 pm

RADIOLOGY IN CROHN'S DISEASE AND ULCERATIVE COLITIS

JAMES A. NELSON, MD
Professor of Radiology
University of Utah College of Medicine
Salt Lake City, Utah

3:20 pm

BREAK

3:30 pm

WHEN MEDICAL TREATMENT GIVES WAY TO SURGERY WHICH OPERATION, WHEN AND WHY?

RUPERT B. TURNBULL, Jr, MD
Santa Barbara, California

III. Approach to Acute Infectious Enterocolitis

4:00 pm

BACTERIAL DYSENTERY AND ANTIBIOTIC COLITIS OR PHYSICIANS CREATE MORE PROBLEMS THAN THEY CURE

J. KENT NELSON, MD
Salt Lake City, Utah

4:10 pm

TRAVELERS DIARRHEA—A RUNNING TRAVELOGUE

EDWIN ENGLERT, Jr, MD
Salt Lake City, Utah

Course No. 2

COMMON PSYCHIATRIC PROBLEMS

DAVID L. McCANN, MD, Moderator

Wednesday (continued)

2:00 pm

TREATMENT OF DEPRESSION

DAVID L. McCANN, MD
Salt Lake City, Utah

2:45 pm

BREAK

3:00 pm

STRESSES FOR DOCTORS AND THEIR FAMILIES

CARLOS N. MADSEN, MD
Salt Lake City, Utah

4:00 pm

HYSTERIA AND SELF-HYPNOTIC DISORDERS

EUGENE L. BLISS, MD
Professor of Psychiatry
University of Utah College of Medicine
Salt Lake City, Utah

THURSDAY, OCTOBER 2

Course No. 3

VULVAR AND VAGINAL INFLAMMATORY DISORDERS

RICHARD M. HEBERTSON, MD, Moderator

9:00 am

HERPES GENITALIS—Diagnosis and Significance

RAYMOND H. KAUFMAN, MD

ERNST W. BERTNER, Professor and Chairman
Department of Obstetrics and Gynecology
Baylor College of Medicine
Texas Medical Center
Houston, Texas

9:40 am

VULVAR DYSTROPHIES—DIAGNOSIS AND TREATMENT

DUANE E. TOWNSEND, MD
Cedars-Sinai Medical Tower
Los Angeles, California

10:10 am

BREAK

10:30 am

DIAGNOSIS AND TREATMENT OF REFRACTORY VAGINITIS

RAYMOND H. KAUFMAN, MD
Houston, Texas

11:15 am

VULVAR INTRAEPITHELIAL NEOPLASIA—DIAGNOSIS AND MODERN THERAPY "LASER"

DUANE E. TOWNSEND, MD
Los Angeles, California

12:00 noon

SPECIAL LUNCH—Grand Ballroom, Hotel Utah
THIRD ANNUAL SKAGGS LUNCHEON

LITTLE ORPHAN ANNIE SYNDROME AND OTHER COPING STYLES IN HEALTH AND CHRONIC DISEASE

RICHARD S. FARR, MD
Senior Staff Physician
National Jewish Hospital and Research Center, and
Professor of Medicine
University of Colorado Health Science Center
Denver, Colorado

Thursday (continued)

Hopes, Helps and Hazards of Estrogen Therapy

2:00 pm

THE HOPES

A. MARSH POULSON, MD
Salt Lake City, Utah

2:30 pm

THE HELPS

WILLIAM R. KEYE, Jr, MD
Salt Lake City, Utah

3:00 pm

BREAK

3:15 pm

THE HAZARDS

RICHARD J. WORLEY, MD
Salt Lake City, Utah

Course No. 4

CORONARY ARTERY DISEASE

ROBERT B. WRAY, MD, Moderator

I. Coronary Bypass Surgery—1980

9:00 am

FROM THE CARDIOLOGIST'S VIEWPOINT

MICHAEL J. PREECE, MD
Salt Lake City, Utah

9:30 am

FROM THE CARDIAC SURGEON'S VIEWPOINT

EDWIN C. McGOUGH, MD
Salt Lake City, Utah

10:00 am

FROM THE PHYSICIAN-PATIENT VIEWPOINT

HIROSHI KUIDA, MD
Professor, Department of Internal Medicine
University of Utah College of Medicine
Salt Lake City, Utah

10:15 am

QUESTIONS

10:30 am

BREAK

II. Myocardial Scans

10:45 am

PRINCIPLES OF MYOCARDIAL SCANNING

DENNIS M. WELCH, MD
Assistant Professor, Department of Radiology
University of Utah College of Medicine
Salt Lake City, Utah

11:05 am

UTILITY OF MYOCARDIAL SCANS

STEVEN C. KLAUSNER, MD
Assistant Professor, Department of Internal Medici
University of Utah, and
Cardiology Division, LDS Hospital
Salt Lake City, Utah

11:25 am

QUESTIONS

Thursday (continued)

III. **Aspirin and Myocardial Infarction**

11:35 am

DOES ASPIRIN PREVENT MYOCARDIAL INFARCTION?

ALLAN H. BARKER, MD
Salt Lake City, Utah

Course No. 5

CONCEPTS OF ADOLESCENT MEDICINE

ARTHUR B. ELSTER, MD, Moderator

9:00 am

CONTRACEPTION FOR ADOLESCENTS

Participants:
DONALD P. ORR, MD
Assistant Professor of Pediatrics and Social Ecology
Director of Adolescent Services
University of California, Irvine
Orange, California

MAURICE G. EMERY, PharmD
Department of Pharmacy Practice
University of Utah Medical Center
Salt Lake City, Utah

JULIAN E. DeLIA, MD
Assistant Professor of Obstetrics and Gynecology
University of Utah College of Medicine, and
Medical Director, Family Planning Program
Utah State Division of Health
Salt Lake City, Utah

10:30 am

BREAK

10:45 am

COMMON MEDICAL AND PSYCHOSOCIAL PROBLEMS OF ADOLESCENTS

DONALD P. ORR, MD
Orange, California

ARTHUR B. ELSTER, MD
Director of Adolescent Medicine
University of Utah College of Medicine
Salt Lake City, Utah

Course No. 6

COMMON DIAGNOSTIC AND THERAPEUTIC PITFALLS IN CHEST DISEASE

LORIMER T. CHRISTENSEN, MD, Moderator

2:00 pm

COMMON DIAGNOSTIC AND THERAPEUTIC PITFALLS IN CHEST DISEASE—CHILDREN

GARY S. RACHELEFSKY, MD
Associate Clinical Professor of Pediatrics and
Co-Director, Pediatric Allergy Clinic
UCLA School of Medicine
Los Angeles, California

3:00 pm

BREAK

3:10 pm

COMMON DIAGNOSTIC AND THERAPEUTIC PITFALLS IN CHEST DISEASE—ADULTS

CHARLES SCOGGIN, MD
Associate Professor, Division of Pulmonary Sciences
University of Colorado Health Sciences Center
Denver, Colorado

Course No. 7

DIAGNOSIS AND TREATMENT OF LOW BACK PAIN

ROBERT F. MOSELEY, MD, Moderator

2:00 pm

NONORTHOPEDIC LOW BACK PAIN

R. CHAD HALVERSEN, MD
Salt Lake City, Utah

2:45 pm

NEUROLOGICAL SOURCES OF PAIN: NERVE IMPINGEMENT SYNDROMES—ETIOLOGIES AND TREATMENT

M. PETER HEILBRUN, MD
Associate Professor of Surgery
University of Utah College of Medicine
Salt Lake City, Utah

3:30 pm

BREAK

Thursday (continued)

3:45 pm

MUSCULOSKELETAL SOURCES OF PAIN: BONE AND JOINT, LIGAMENT, MUSCLE—ETIOLOGIES AND TREATMENT

STANLEY J. BIGOS, MD
Department of Orthopedics
University of Utah College of Medicine
Salt Lake City, Utah

Thursday (continued)

4:30 pm

EMOTIONAL SOURCES OF PAIN: EMOTIONAL-PSYCHIATRIC AND SOCIAL—ETIOLOGIES AND TREATMENT

JAMES R. WHITTEN, MD
Salt Lake City, Utah

2:00 pm-5:00 pm THURSDAY, OCTOBER 2
9:00 am-12:00 noon FRIDAY, OCTOBER 3

Course No. 8 FAMILY PRACTICE WORKSHOP—MINI COURSES

ROBERT M. PAYNE, MD and ROLF K. NALEY, MD, Co-Moderators

Subjects	Course Director	Time Thursday	Time Friday
ARTHRITIS	H. JAMES WILLIAMS, MD Salt Lake City, Utah	2:00-3:00 pm	9:00-10:00 am
PSYCHIATRY	DAVID WOOD, MD Salt Lake City, Utah	3:00-4:00 pm	10:00-11:00 am
OPHTHALMOLOGY	GEORGE C. PINGREE, MD Murray, Utah	4:00-5:00 pm	
	RICHARD A. ALDOUS, MD Salt Lake City, Utah		11:00-12:00 noon
UROLOGY	DOUGLAS S. DAHL, MD Salt Lake City, Utah	2:00-3:00 pm	9:00-10:00 am
OBSTETRICS/GYNECOLOGY	ANTHON E. ANDERSON, MD Murray, Utah	3:00-4:00 pm	10:00-11:00 am
ORTHOPEDICS	DAVID J. HOWE, MD Salt Lake City, Utah	4:00-5:00 pm	11:00-12:00 noon

FRIDAY, OCTOBER 3

Course No. 9

PERSPECTIVES IN HYPERTENSION

H. ALLAN BLOOMER, MD, Moderator

9:00 am

The first portion of the course will be directed to short lectures on the recognition, evaluation and treatment of hypertension in an office setting.

EVALUATION OF THE HYPERTENSIVE PATIENT

RICHARD G. LAMBERT, MD
Salt Lake City, Utah

DRUG TREATMENT OF HYPERTENSION

H. ALLAN BLOOMER, MD
Salt Lake City, Utah

SIDE EFFECTS OF THERAPY

RICHARD G. LAMBERT, MD
Salt Lake City, Utah

RESISTANT HYPERTENSION

H. ALLAN BLOOMER, MD
Salt Lake City, Utah

HYPERTENSION IN CHILDREN AND ADOLESCENTS

RICHARD L. SIEGLER, MD
Salt Lake City, Utah

Course No. 10

OPHTHALMOLOGY TODAY

GEORGE H. PINGREE, MD, Moderator

9:00 am

DIFFERENTIAL DIAGNOSIS OF SUPERFICIAL LESIONS OF THE CORNEA AND LIMBUS

THOMAS H. PETTIT, MD
Professor of Ophthalmology
Chief, Corneal External Disease Service
Jules Stein Eye Institute
UCLA School of Medicine
Los Angeles, California

Friday (continued)

10:00 am

INTRAOCULAR LENS SAFETY, EFFICACY AND ALTERNATIVES

RANDALL J. OLSON, MD
Chairman, Department of Ophthalmology
University of Utah College of Medicine
Salt Lake City, Utah

11:00 am

GENERAL DISCUSSION: Questions and Answers

Course No. 11

TREATMENT OF NEUROLOGICAL DISORDERS

JACK H. PETAJAN, MD, Moderator

9:00 am

EPILEPSY

FUMISUKE MATSUO, MD
Associate Professor of Neurology
University of Utah College of Medicine
Salt Lake City, Utah

9:45 am

HEADACHE AT ALL AGES

JOEL A. THOMPSON, MD
Assistant Professor of Pediatrics
Primary Medical Center
Salt Lake City, Utah

10:30 am

BREAK

10:45 am

MOVEMENT DISORDERS

FRED A. ZITER, MD
Professor of Neurology
University of Utah College of Medicine
Salt Lake City, Utah

11:15 am

MYASTHENIA GRAVIS, MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE DISORDERS

JACK H. PETAJAN, MD
Professor of Neurology
University of Utah College of Medicine
Salt Lake City, Utah

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DONALD D. TRUNKEY, MD, San Francisco, CA
Associate Professor of Surgery
University of California, San Francisco

- **The Pathophysiology of Shock**

PHILIP NADER, MD, Galveston, Texas
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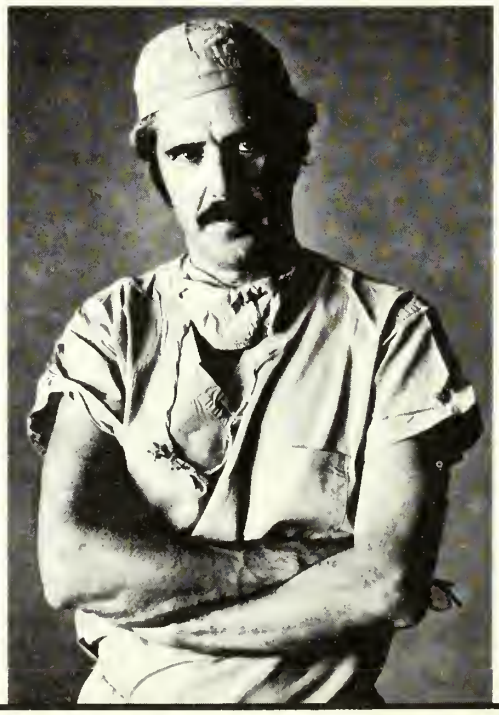

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DISTRICT HEALTH OFFICER, PUBLIC HEALTH: physician experienced in public health and preventive medical programs: to direct and provide patient care in primary care, venereal disease, family planning, child health, hypertension and related preventive medical clinics in northern Santa Barbara County. Send résumé to R. Marvan, MD, 300 San Antonio Road, Santa Barbara, CA 93110.

FAMILY PRACTITIONER. Santa Barbara County Department of Health Care Services. Primary care practice in beautiful north Santa Barbara County. Physician to work in community based clinics. Prefer bilingual ability English-Spanish. Salary $50,794 or $56,438 depending on board certification. Contact: Robert Marvan, MD, Director, Clinical Services, 300 San Antonio Road, Santa Barbara, CA 93110.

PUBLIC HEALTH PHYSICIAN to direct contagious disease control program Santa Barbara County. Primary focus will be placed on clinical participation and directorship of public health clinics. Requirements: California license, epidemiology skills, residency training or 2 years' experience in public health. Salary $50,794 or $56,438 depending on board certification. Submit CV and names and addresses of 3 references to Robert Marvan, MD, Director, Clinical Services, 300 San Antonio Road, Santa Barbara, CA 93110.

HEALTH CENTER DIRECTOR—Director of Health Services. University of California, Santa Cruz. Serving a campus community of 6,000 students and 2,000 faculty and staff. Responsible for primary care outpatient and inpatient services, psychiatric services, environmental and occupational health and safety programs. Requires California license or ability to obtain prior to employment; knowledge and/or experience of medical and paramedical services, medical records and patient care documentation, health insurance benefit structures, management theory and practice; Board qualified in a clinical or preventive medicine specialty. Prefer candidates with demonstrated successful administrative, clinical and campus health care experience. Salary: $4,256-$5,152/month plus excellent benefits. Apply: Personnel Office, University of California, Santa Cruz, CA 95064. Closing date: 10-23-80. This is a reopened position.

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FAMILY PRACTICE PHYSICIAN needed to share clinic. Well established practice in beautiful Southern Utah. Reply Earl Plunkett, MD, Box 489, Hurricane, UT 84737. Phone (801) 635-4688.

SITUATIONS WANTED

FAMILY PRACTITIONER, board certified, age 60, vigorous health. Extremely successful practice and clinic recently sold. Looking for association in Southern California which would allow frequent time off for vacation and travel (3 to 6 months per year). Innovative, energetic, computer expertise, medical school faculty appointment. Reply Box 6137, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, 45, certified AP-CP, excellent references, seeks relocation to San Francisco-San Jose area for permanent full-time or part-time practice. Box 6110, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN with 10 years experience in preventive and occupational medicine and postgraduate training for 4 years, seeks position in San Francisco/Bay Area in medical outpatient clinic. Write Box 6020, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL SURGEON, surgical oncologist, head and neck surgeon: 38-year-old university and Memorial Sloan-Kettering trained, Board Certified American with extensive teaching and private practice experience wishes to relocate. Box 6133, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OTOLARYNGOLOGIST, certified, age 61. Experienced in all aspects, otology, head and neck and cosmetic surgery. Seeks part or full time position, salaried or group. Box 6142, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

AMERICAN BOARD ELIGIBLE UROLOGIST, finishing Urology Residency in June, 1981, available for solo or group practice in July-August, 1981. Would be willing to work in Emergency Medicine. Write Box 6144, Western Journal of Medicine, 731 Market St, San Francisco, CA 94103.

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SITUATIONS WANTED

TECHNICAL WRITER—Physician with medical and educational experience and technical writing training available for technical writing and editing. Clare Harper, MD, 120 Via Lerida, Greenbrae, CA 94904, (415) 461-4700.

PULMONARY INTERNIST, University trained, ABIM, trained all phases of pulmonary medicine; seeks practice opportunity; available July 1981. Box 6141, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

37-YEAR-OLD MALE. AFFP certified with 10 years experience, seeks family practice group association/partnership in Oakland/East Bay area. Interested in holostic medicine. Available immediately. Box 6143, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, 49, certified AP-CP, broad experience and excellent references, California and Oregon licenses. Available immed. (714) 287-5539.

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BUYING or SELLING any type Medical Practice contact California Professional Practices, 2555 Huntington Drive, Suite D, San Marino, CA 91108. (213) 796-9262, Eve (213) 355-3983 and 21 Altamount Dr., Orinda, CA 94563. (415) 376-0762.

INTERNAL MEDICINE—quality practice. Hollywood-Wilshire area, L.A.—5 min. to excellent residential areas and to major hospitals. Net earnings per hour 6 times national average for internists. Will stay to introduce new doctor. Please write, Box 6139, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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FAMILY PHYSICIAN, ABFP, mature, broad office experience, med. school faculty appt. available for locum tenens work in Los Angeles, San Diego or Palm Springs areas. (303) 377-9373.

TRANSLATORS (FREELANCE)

URGENTLY NEEDED for med./chem. texts, all languages. SCITRAN, Box 5456, Santa Barbara, CA 93108.

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ANESTHESIOLOGY

October 3-5—**Anesthesia Specialties.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Friday-Sunday. 10½ hrs. $90, AEF member; $165, nonmember. Contact: Walter H. Comer, MD, AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

October 26-28—**Anesthesia and Cardiopulmonary Disease.** Calif. Society of Anesthesiologists at Del Monte Hyatt, Monterey. Sunday-Tuesday. 11 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

November 8-9—**American Society of Anesthesiologists—Refresher Course.** Hilton, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

December 12-14—**Anesthesia: Before and After.** Tucson Hospitals Medical Education Program at Canyon Hotel, Palm Springs. Friday-Sunday. $150. Contact: James P. Angiulo, MD, Kino Community Hosp., 2800 E. Ajo Way, Tucson, AZ 85713.

January 6-10—**Anesthesia Update.** UCSD at Hotel del Coronado, Coronado. Tuesday-Saturday. 20 hrs. $250.

January 23-25—**Pediatric Anesthesiology—19th Clinical Conference.** Childrens Hospital of Los Angeles at Marriott Hotel, Los Angeles. 15 hrs. $165. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

CANCER

October 9-11—**American Cancer Society.** Hilton, Los Angeles. Thursday-Saturday. Contact: N. G. Bolliglieri, MD, ACS, 777 Third Ave., New York 10017.

October 24-26—**Cancer and Enzymes.** UCSD at Vacation Village, San Diego. Friday-Sunday.

October 27-29—**4th Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. 22 hrs. $300. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

November 6-8—**Current Concepts in Cancer Diagnosis.** UCLA. Thursday-Saturday.

November 7-8—**Cancer Prevention and Screening.** Claire Zellerbach Saroni Tumor Institute of Mt. Zion Hospital and Medical Center at Holiday Inn on Union Square, San Francisco. Friday-Saturday. 10 hrs. $125 before September 15; $150 thereafter. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

November 15—**Current Advances in Cancer Care.** Eden Hospital and American Cancer Society, Alameda Chapter, at Hilton Hotel, Oakland. Saturday. Contact: Joseph C. Beck, MD, Dept. of Radiology, Eden Hosp., 20103 Lake Chabot Rd., Castro Valley 94546. (415) 537-1234, ext. 252.

November 21—**Modern Management of Anorectal Carcinoma.** USC Cancer Center and American Cancer Society at Bonaventure Hotel, Los Angeles. Friday. Contact: Robert J. McKenna, MD, Dir., USC Comprehensive Cancer Ctr., 1721 Griffin Ave., Los Angeles 90031. (213) 226-4041.

January 22-24—**Current Concepts in Cancer Diagnosis.** UCLA at Century Plaza Hotel, Los Angeles. Thursday-Saturday.

January 23-24—**Cancer Update 1981.** Peralta Hospital at Goodman's Hall, Jack London Square, Oakland. Friday-Saturday. 10 hrs. Contact: Susan Ford, Education and Training Dept., Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 2327.

January 24-25—**Current Approaches to Radiation Oncology.** UCSF at Sir Francis Drake Hotel, San Francisco. Saturday-Sunday.

February 12-13—**Controversies in Lung Cancer.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 14 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 28-March 1—**Recent Advances in Cancer Diagnosis.** UCLA. Saturday-Sunday.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

EMERGENCY MEDICINE

September 18—**Abdominal Trauma.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 3-4—**Postgraduate Institute on Emergency Medicine—5th Annual.** UCLA at Miramar-Hilton, Santa Monica. Friday-Saturday. 14 hrs. $170.

October 9-February 5—**Management of Pre-Hospital Emergencies.** UCLA. 5 Thursday evenings.

October 13-17—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

October 16—**Dermatology in the Emergency Department.** UCSD. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 20-31—**Intensive Review of Emergency Medicine.** USC. Two weeks.

November 3-5—**Postgraduate Institute for Emergency Physicians, Symposium IV.** UCSD at Hilton, San Diego. Monday-Wednesday.

November 20—**Clinical Pharmacology in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

December 8-12—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

December 10—**Emergency Medicine.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

January 15-20—**Emergency Medicine.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Tuesday.

January 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

February 16-20—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

MEDICINE

September 15-17—**3rd Annual Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Monday-Wednesday. 20 hrs. $200.

September 17-18—**48th Annual Fall Symposium and 13th Annual George C. Griffith Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Wednesday-Thursday. 13 hrs. $100, member of any heart assn.; $125, nonmember. Contact: Mary Frances Flynn, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231, ext. 59.

September 18-19—**Advances in Cardiovascular Theraples.** UCD at Sahara Tahoe, Stateline. Thursday-Friday. 9 hrs. $20.

September 24—**Renal Conference.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

September 25-26—**Annual Physicians' Symposium.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Kari Olila, AHA, 421 Powell St., San Francisco 94102. (415) 433-2273.

September 25-26—**Pacific Southwest Conference on High Blood Pressure Control.** American Heart Assn., Calif. Dept. of Health Services, etc. at New Otani Hotel, Los Angeles. Thursday-Friday. $45. Contact: Pacific Southwest Conf. on High Blood Pressure Control, 5820 Wilshire Blvd., Suite 303, Los Angeles 90036. (213) 937-6334.

September 25-28—**American Society of Ophthalmologic and Otolaryngologic Allergy—Annual Meeting.** Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: William King, MD, 1415 3rd St., Corpus Christi, TX 78404.

September 26-27—**American Society of Internal Medicine.** Islandia Hyatt, San Diego. Friday-Saturday. Contact: ASIM, 2550 M St. NW, Suite 620, Washington, DC 20037.

September 26-27—**Dermatology for the Primary Care Physician.** UCD at Holiday Inn, Napa Valley. Friday-Saturday. 11½ hrs.

September 26-28—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Hyatt on Union Square, San Francisco. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

September 27—**Management of Common Lung Problems.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 6½ hours. $35.

September 27-28—**Recent Advances in Cardiology.** The Center Foundation, Los Angeles. Saturday-Sunday. 12 hrs. $250. Contact: Michael Urban, Dir., Cont. Med. Ed., The Center Fndn., 7165 Sunset Blvd., Los Angeles 90046. (213) 874-3136.

October 1-December 17—**Cardiology.** UCLA. Wednesday evenings.

October 4—**Third Annual Heart Symposium.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. 8 hrs. Contact: Carla Weis, Northridge Hosp. Community Relations Office, 18300 Roscoe Blvd., Northridge 91328. (213) 885-5339.

October 4-11—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

October 8—**Modern Therapy for Common Dermatologic Problems.** LLU. Wednesday. 4 hrs. $30.

October 10-11—**Mycology Review.** STAN. Friday-Saturday. A course for residents in dermatology and pathology. 14 hrs. Contact: Paul H. Jacobs, MD, Dermatology Dept., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

October 10-12—**Chest Disease Symposium.** The Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

October 11—**Allergy and Immunology in Office Practice.** PMC. Saturday. 6 hrs.

October 13-17—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs. $290.

October 15-16—**Advanced Electrocardiography.** St. Francis Medical Center, Lynwood. Wednesday-Thursday. 12 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

October 18-19—**Current Concepts in Cardiology and Hypertension.** Kaiser Foundation Hospital at Red Lion Inn, Sacramento. Saturday-Sunday. 8 hrs. $10. Contact: Cheryl English, Med. Ed. Office, Kaiser Fndn. Hosp., 2025 Morse Ave., Sacramento 95825. (916) 486-5965.

October 18-25—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $325.

October 23-28—**Pacific Dermatologic Association.** Hilton Riviera, Palm Springs. Thursday-Tuesday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno, NV 89509. (702) 323-2461.

October 27-30—**Practical Electrocardiography Course for Primary Physicians.** Memorial Hospital Medical Center-UCI Center for Health Education at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: Center for Health Education. 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 29—**Endocrine Review.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Dept. of Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

October 30-November 1—**Cardiology Update 1980.** American College of Cardiology at Del Monte Hyatt, Monterey. Thursday-Saturday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 30-November 2—**California Society of Internal Medicine—Annual Meeting.** Doubletree Inn, Monterey. Thursday-Sunday. Contact: Carol Parlette, Exec. Dir., CSIM, 703 Market St., 1412 Central Tower, San Francisco 94103. (415) 362-1548.

November 1—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

November 5-8—**American Thyroid Association.** Holiday Inn at the Embarcadero, San Diego. Wednesday-Saturday. Contact: Dorothy Hickler, Exec. Sec., ATA, Univ. of MA Medical Ctr., 55 Lake Ave. N., Worcester, MA 01605. (617) 856-3115.

November 8—**Second Annual Winter Symposium on Cardiology.** Bay General Community Hospital at Hotel del Coronado, Coronado. Saturday. 10 hrs. $65. Contact: Medical Staff Office, Bay Gen. Community Hosp., 435 H St., Chula Vista 92010. (714) 420-8182, ext. 233 or 241.

November 12—**Peptic Ulcer—Its Diagnosis and Treatment in the 1980's.** LLU. Wednesday. 4 hrs. $30.

November 13-15—**Allergy/Immunology for the Practicing Physician.** UCSF. Thursday-Saturday. 15 hrs. $150.

November 17-19—**International Symposium on Status Epilepticus.** UCLA at Miramar-Sheraton, Santa Monica. Monday-Wednesday. 20 hrs.

November 29-December 1—**Advances in Heart Disease 1981.** American College of Cardiology at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 1-3—**Cardiovascular-Pulmonary Update for the Practicing Physician.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 19 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

December 5—**Recognition and Management of Bleeding Disorders.** Children's Hospital Medical Center of Northern Calif. at Sir Francis Drake Hotel, San Francisco. Friday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

December 5-7—**Cardiac Rehabilitation.** International Medical Education Corp. at Wilshire Hyatt, Los Angeles. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

December 5-7—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Desert Inn, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

December 6-7—**Neurology for the Primary Care Physician.** UCLA. Saturday-Sunday.

December 10—**Collagen Disease—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $30.

December 11-14—**Intensive Care for Neurological Trauma and Disease: A New Decade.** Comprehensive Central Nervous System Injury Foundation and Univ. of Miami at Vacation Village, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Comprehensive CNS Injury Fndn., P.O. Box 9494, San Diego 92109.

December 13—**Endocrinology and Metabolism in the 80's: A New Frontier.** Daniel Freeman Hospital Medical Center at Hyatt House, Los Angeles. Saturday. 6 hrs. $100. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp. Med. Ctr., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 3427.

January 9-11—**Debates, Controversies and Concepts in the Treatment of the High Risk Patient.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Friday-Sunday. 19 hrs. $225. Contact: Lore Kahane, Rm. 2049, Cedars-Sinai Med. Ctr., P.O. Box 48750, Los Angeles 90048. (213) 855-5547.

January 10-11—**Practical Pulmonary Diseases.** UCLA. Saturday-Sunday.

January 14—**Arrhythmias—Their Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $30.

January 24—**Cardiology Seminar—10th Annual.** Fresno Community Hospital and Medical Center. Saturday. Contact: Joann Ellis, Ed. and Training Dept., Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

January 26-28—**Practical Management of Bronchial Asthma and Asthmatic Bronchitis.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

January 30-31—**Cardiology Update — 1981 — The Changing Scene.** St. Francis Medical Center at Bonaventure Hotel, Los Angeles. Friday-Saturday. 14 hrs. Contact: Allan Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603- 6174.

February 2-4—**Clinical Echocardiography—1981.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 3-6—**Pediatric Cardiology.** USC at Gene Autry Hotel, Palm Springs. Tuesday-Friday.

February 4—**Endocrine Disorders.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

February 4-6—**Western Section of the Society for Investigative Dermatology, Western Section of American Federation for Clinical Research, Western Society for Clinical Research.** Carmel. Wednesday-Friday. Contact: Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, NJ 08086.

February 11-13—**Recent Advances in Neurology.** UCSF. Wednesday-Friday.

February 14—**Sixth Annual Liver Conference: Cirrhosis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 14-15, 21-22—**Dermatology.** UCLA. Two weekends.

February 16-18—**Recent Advances in Clinical Endocrinology.** UCSF at Sir Francis Drake Hotel, San Francisco. Monday-Wednesday.

February 18-20—**Neuro-Orthopedic Screening.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 18-April 22—**Gastroenterology.** UCLA. Wednesday evenings.

February 19-21—**Immunology.** STAN. Thursday-Saturday. 13 hrs. $245.

February 19-21—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Fndn., American Heart Assn., American Lung Assn., Nat'l Critical Care Institute of Education, Vascular Disease Fndn. at Mission Bay Hilton, San Diego. Thursday-Saturday. $250. Contact: CREF, P.O. Box 33185, San Diego 92103.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** Scripps Clinic and Research Fndn. at Vacation Village, San Diego. Monday-Thursday. 25 hrs. $290. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 25—**Hospital Acquired Infections.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

OBSTETRICS AND GYNECOLOGY

September 25-27—**Advances in Obstetrics.** UCSF. Thursday-Saturday.

November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** UCSD at Bahia Hotel, San Diego. Wednesday-Friday. 19 hrs. $185. Contact: Ronald W. Coen, MD, UCSD Sch. of Med., C-019, La Jolla 92093. (714) 452-4424.

December 5-7—**5th Annual Symposium on Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort. Friday-Sunday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 10-17—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

January 14-17—**Postgraduate Course on Basic and Advanced Gyn Urology: Theory and Practice.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Wednesday-Saturday. 20 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 25-30—**Obstetrics-Gynecology Update: 1981.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

January 26-30—**10th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday. 36 hrs. $400.

February 7-8—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society. Saturday-Sunday. Contact: Dee Davis, Exec. Sec., LAOGS, 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

PEDIATRICS

September 18-20—**Pediatric Urology.** UCD at Holiday Inn, Napa Valley. Thursday-Saturday. 12 hrs.

October 3-4—**Pediatric Topics: Neonatology.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs. $85.

October 8-9—**37th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: L.A. Pediatric Soc., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

October 15—**Pediatric Urology.** See Surgery, October 15.

October 25—**Hearing Impaired Child.** Peninsula Hospital, Burlingame. Saturday. Contact: Susan Norrell, c/o Radiology Dept., Peninsula Hosp., 1783 El Camino Real, Burlingame 94010. (415) 697-4061, ext. 479.

October 25-November 1—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education and L.A. Pediatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $200. Contact: Center for Health Education, MHMC, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 27-31—**4th Annual Pediatrics for the Practitioner—A Pediatric Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday. 21 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 1—**Pediatric Dermatology Seminar.** See Medicine, November 1.

November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** See Obstetrics-Gynecology, November 5-7.

November 15—**Pediatric Ophthalmology for the Primary Care Physician.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 4 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

November 21-24—**Pediatric Update.** American Academy of Pediatrics, Calif. Chapters 1, 2 and 3, at Hilton Hotel, Las Vegas. Friday-Monday. 15 hrs. $175, members; $200, nonmembers. Contact: AAP, Chap. 2, P. O. Box 2134, Inglewood 90305.

December 3-7—**5th Annual Pediatric Seminar.** Los Angeles Pediatric Society at Kahala Hilton, Honolulu. Wednesday-Sunday. 11 hrs. $75. Contact: Los Angeles Pediatric Soc., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

December 5-7—**Children and Their Skeletons: A Practical Approach.** UCD at Hyatt Del Monte, Monterey. Friday-Sunday.

February 3-6—**Pediatric Cardiology.** See Medicine, February 3-6.

PSYCHIATRY

October 11-12—**The Healing Brain II.** UCSF at Sheraton Palace, San Francisco. Saturday-Sunday. $95. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

October 25—**Cognitive Prospectives in Psychiatry.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 14-16—**Infant Psychiatry III: Pathological Infants and Their Parents; Pathological Parents and Their Infants.** UCSF. Friday-Sunday.

November 17-21—**Group Therapy.** UCSF. Monday-Friday.

January 25-31—**7th Annual Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. One week. 26 hrs.

RADIOLOGY AND PATHOLOGY

September 1980-August 1981—**Current Surgical Pathology Practice.** Naval Regional Medical Center at Oak Knoll Naval Hospital, Oakland. Fridays; 7:45-9:00 a.m. Contact: R. W. Poley, Dept. of Pathology, Naval Regional Med. Ctr., Oakland 94627.

September 15-17—**3rd Annual Postgraduate Course in Medical Mycology (Dermatomycology).** See Medicine, September 15-17.

September 22-26—**Diagnostic Hematology.** American Society of Clinical Pathologists at Sheraton-San Diego Airport. Monday-Friday. 32½ hrs. $600, ASCP members; $700, Nonmembers. Contact: ASCP Educational Ctr., 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

September 27-October 4—**Diagnostic Radiology.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $290.

October 10-11—**Mycology Review.** See Medicine, October 10-11.

October 10-12—**Society of Nuclear Medicine—5th Annual Western Regional Meeting.** Airport Marriott, Los Angeles. Friday-Sunday. Contact: SNM, P.O. Box 40279, San Francisco 94140. (415) 647-5909.

October 11-19—**5th Annual International Body Imaging Conference.** West Park Hospital, Canoga Park, at Kauai Surf Hotel, Kauai, Hawaii. 9 days. 25 hrs. $335. Contact: West Park Hospital, Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 24-26—**Advances in Immunopathology.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Friday-Sunday. 17 hrs. $120. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

October 28-30—**Gram Negative Organisms: An Approach to Identification.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Thursday. 21 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 1—**Radiology for Clinicians—1980.** Cedars-Sinai Medical Center at Century Plaza, Los Angeles. Saturday. 7 hrs. $80. Contact: Lore Kahane, Rm. 2049, Cedars-Sinai Med. Ctr., P.O. Box 48750, Los Angeles 90048. (213) 855-5547.

December 13-14—**Using the Clinical Lab.** UCLA. Saturday-Sunday.

January 19-23—**Interventional Radiologic Techniques: Computed Tomography and Ultrasonography.** UCSF at Fairmont, San Francisco. Monday-Friday. $350.

January 19-24—**Review Course in Clinical Ob, Gyn, and Histological Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Monday-Saturday. 41 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 21-23—**8th Annual Postgraduate Course in Genitourinary Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 22½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 24-31—**International Diagnostic Radiology Conference.** UCSF at Maui Surf Hotel, Maui, Hawaii. UCSF. One week.

February 4-6—**Recent Progress in Diagnostic Laboratory Immunology.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 24 hrs. $250. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 9-12—**Molecular Basis of Cell-Cell Interaction.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Monday-Thursday. 24 hrs. $165. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 11—**Neuroradiology—Its Use, Indications and Values in Strokes, Tumors and Head Trauma.** LLU. Wednesday. 4 hrs. $30.

February 18-20—**Anaerobic Bacteriology Methods.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 15 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27-March 1—**Neuroradiology.** USC. Friday-Sunday. 20 hrs. $200.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

September 18-20—**Pediatric Urology.** See Pediatrics, September 18-20.

September 19-20—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

September 25-28—**Cost Effective Urological Diagnosis and Treatment.** Western Section, Am. Urological Assn. and AUA at Marriott's Rancho Las Palmas Resort, Palm Springs. Thursday-Sunday. Contact: Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

September 26-27—**Vitrectomy.** UCSD at Vacation Village, San Diego. Friday-Saturday.

September 27—**Medical Malpractice in Ophthalmology. A Review of Common Diagnostic and Therapeutic Errors.** Estelle Doheny Eye Foundation, Los Angeles; Course coordinators Albert Tashma, MD and Ronald E. Smith, MD. Contact: Nancy Call, Estelle Doheny Eye Foundation, 1355 San Pablo Street, Los Angeles, CA 90033. (213) 224-7752.

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September 28-October 2—**American Academy of Otolaryngology.** Convention Center, Anaheim. Sunday-Thursday. Contact: AAO, 15 Second St. SW, Rochester, MN 55901.

October 2-3—**Problems in Vascular Surgery—Review and Update.** Cedars-Sinai Medical Center at Century Plaza, Los Angeles. Thursday-Friday. 14 hrs. $200. Contact: Lore Kahane, Rm. 2049, Cedars-Sinai Med. Ctr., P.O. Box 48750, Los Angeles 90048. (213) 855-5547.

October 3-5—**State of the Art: Recent Advances in Head and Neck Surgery.** Institute for Medical Education and Research at Islandia Hyatt, San Diego. Friday-Sunday. 14 hrs. $200. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126 or (714) 294-5910.

October 9-11—**New Techniques in Hip Resurfacing and Replacement—In-depth Course and Workshop.** UCLA. Thursday-Saturday.

October 15—**Pediatric Urology—8th Annual Postgraduate Conference.** Los Angeles Urological Society at Marriott Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Trudy Mackel, LAUS, P.O. Box 836, Lomita 90717. (213) 326-7418.

October 24-25—**Cataract Surgery and Intraocular Lenses Course: Planned Extracapsular, Phacoemulsification and Intracapsular Techniques.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $350. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

October 25-November 1—**Operative Arthroscopy.** UCLA at Maui, Hawaii. One week.

November 6-8—**Sterling Bunnell Memorial Lectureship.** UCSF, Dept. of Orthopaedic Surgery. Thursday-Saturday. 18 hrs. $200.

November 7-8—**Leg Amputations and Their Rehabilitation.** PMC at Hyatt on Union Square, San Francisco. Friday-Saturday. 12 hrs. $185.

November 14-15—**Vitrectomy/Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs. $450.

December 3-4—**6th Annual Meeting and Scientific Symposium —Lyman A. Brewer, III, International Surgical Society—Controversies in the Management of Coronary Heart Disease.** White Memorial Medical Center at Hilton, Los Angeles. Wednesday-Thursday. Contact: Dr. Howard Whigham, Dir., Research and CME, White Mem. Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033.

December 6—**Practical Workshop on Surgery of the Eyelids, Lacrimal System and Orbit.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $275. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

December 11-13—**Trauma.** No. Calif. Chap. of the Committee on Trauma of Am. College of Surgeons at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. Contact: Donald D. Trunkey, MD, Chief of Surgery, S.F. Gen. Hosp., 1001 Potrero Ave., San Francisco 94110.

December 11-14—**Intensive Care for Neurological Trauma and Disease: A New Decade.** See Medicine, December 11-14.

December 12-13—**Ophthalmology Update.** UCD, UCSF, PMC, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

January 9-11—**Debates, Controversies and Concepts in the Treatment of the High Risk Patient.** See Medicine, January 9-11.

January 10—**Photocoagulation Therapy.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

January 23-24—**Third Annual Postgraduate Course in Surgery.** UCD at Point West Hotel, Sacramento. Friday-Saturday. 14 hrs. $85.

January 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

January 25-30—**Assembly in Surgery—4th Annual.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sunday-Friday. 28 hrs.

February 4-6—**Current Thinking in the Management of Ocular and Adnexal Tumors.** UCSF. Wednesday-Friday.

February 5-7—**Aesthetic Rhinoplasty and Nasal Reconstruction.** UCLA. Thursday-Saturday.

February 6-8—**National Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery and American Society for Dermatologic Surgery at Ramada Inn, Beverly Hills. Friday-Sunday. Contact: Drs. Richard Fleming, Toby Mayer, Peter Goldman, 9730 Wilshire Blvd., Ste. 216, Beverly Hills 90212.

February 8-10—**The Mandible: Surgical Treatment of Congenital and Acquired Deformities.** UCLA. Sunday-Tuesday.

February 14-20—**Neurological Surgery of the Ear and Skull Base—3rd International Workshop.** Ear Research Institute at Newporter Inn, Newport Beach. One week. 32 hrs. $500. Contact: Derald E. Brackmann, MD, Neurological Workshop, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

September 22-26—**Primary Care: Current Management of Common Office Problems.** UCSF. Monday-Friday.

September 24-27—**Society for Computer Medicine.** Hilton, San Diego. Wednesday-Saturday. Contact: SCM, 1901 N. Ft. Myer Dr., Ste. 602, Arlington, VA 22209.

September 24-28—**Human Dimensions in Medicine.** UCSD at Vacation Village, San Diego. Wednesday-Sunday.

September 25—**Venereal Disease.** Calif. Venereal Disease Controllers' Assn. and CMA at Tiburon Lodge, Tiburon. Thursday. Contact: Manuel De Pinna, CMA.

September 25-December 4—**Recent Advances in Alcoholism: Biological and Behavioral Effects.** UCI. Thursdays; 7:00-10:00 p.m. 30 hrs. Contact: UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

September 26—**Preparing the Chronically Ill Patient for "Going Home."** Mt. Zion Hospital and Medical Center at St. Mary's Cathedral, San Francisco. Friday. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

September 26-27—**Introduction to Microcomputers.** PMC at Lone Mountain Campus-USF. Friday-Saturday. 12 hrs. $395.

September 29-October 1—**Alcoholism and Chemical Dependency Treatment—Where Do We Go From Here?** Scripps Memorial Hosp. at Vacation Village, San Diego. Monday-Wednesday. 15 hrs. $175. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110.

October 3-4—**Medicine in the 80's—State of the Art.** Unity Church of Hawaii, Hawaii Medical Assn., Univ. of Hawaii at Prince Kuhio Hotel, Honolulu. Friday-Saturday. 7 hrs. Contact: Unity Church of Hawaii, 3608 Diamond Head Circle, Honolulu 96815. (808) 735-4436.

October 10-11—**Acute Care and Critical Care in Medicine.** Southern Calif. Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

October 11—**Ophthalmology for the Family Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

October 11-12—**The Healing Brain II.** UCSF at Sheraton Palace, San Francisco. Saturday-Sunday. $95. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

October 13-16—**Fifth Annual Family Practice Update.** LLU. Monday-Thursday. 31 hrs. $200.

October 13-17—**Hawaii Medical Association—124th Annual Meeting.** Pacific Beach Hotel, Waikiki. Monday-Friday. Contact: HMA, 320 Ward Ave., Ste. 200, Honolulu 96814. (808) 536-7702.

October 15-18—**24th Annual Western Occupational Health Conference.** Western Occupational Med. Assn. at Hotel del Coronado, Coronado. Wednesday-Saturday. Contact: Joe Donovan, WOHC, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 16-18—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 24—**Patient Care—Challenging the Image.** St. Francis Medical Center at Sheraton Hotel, Anaheim. Friday. 7 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

October 24-25—**Geriatric Medicine Today.** Western Div., Am. Geriatrics Soc., at Hyatt Regency, San Francisco. Friday-Saturday. Contact: AGS, Western Div., 13220 105th Ave., Bldg. B, Rm. 61, Sun City, AZ 85351.

October 24-26—**In Pursuit of Wellness.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

October 25-26—**Eight Common Problems.** UCLA. Saturday-Sunday.

October 28-31—**American Academy of Occupational Medicine.** Hyatt Regency, San Francisco. Tuesday-Friday. Contact: AAOM, 150 N. Wacker Dr., Chicago 60606.

October 30-November 1—**Postgraduate Institute on Nutrition.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 31-November 1—**Understanding Cross-Cultural Differences in Illness and Among Hispanic and Indochinese Immigrants/Refugees.** UCLA. Friday-Saturday. $75.

November 2-5—**California Academy of Family Physicians—Annual Scientific Assembly.** Disneyland Hotel, Anaheim. Sunday-Wednesday. Contact: William W. Rogers, Exec. Sec., CAFP, 9 First St., Rm. 900, San Francisco 94105. (415) 982-6091.

November 3-7—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $275.

November 3-7—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $290.

November 5—**Sexuality.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Medical Center, 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

November 6-9—**Practical Hypnosis: Introductory and Intermediate Courses.** San Diego Society of Clinical Hypnosis and UCSD. Thursday-Sunday. 21 hrs. $290. Contact: UCSD.

November 8—**Psychiatry for the Primary Care Physician: Close Encounters of the Troubling Kind.** UCD at Red Lion Inn, Sacramento. Saturday. 7½ hrs. $65.

November 8-9—**Cross Cultural and Trans Cultural Issues in Family Health Care.** UCSF. Saturday-Sunday. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

November 13-15—**Biofeedback and Family Practice.** UCLA and Biofeedback Society at San Jose. Friday-Saturday. Contact: UCLA.

November 13-15—**Medical Aspects of Products Liability.** UCSF. Thursday-Saturday.

November 15—**Criteria for Evaluating Pseudoscience, Cults and Holistic Medicine.** San Jose State University. Saturday. 8 hrs. $40. Contact: Susan M. Grube, MPH, Cont. Ed., San Jose State Univ., Washington Sq., San Jose 95192. (408) 277-3778.

November 15-16—**Fourth Annual National Symposium on Aging.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

November 16—**Frontiers in Medicine—12th Annual Symposium.** UCLA and Granada Hills Community Hospital at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344.

November 21-23—**Sports Medicine: The Physician and the Athlete.** UCD at Marriott Inn, Berkeley. Friday-Sunday. 12 hrs. $140.

November 21-25—**Gerontological Society—Annual Scientific Meeting.** Town and Country Hotel, San Diego. Friday-Tuesday. Contact: Dr. Eugene J. Towbin, VA Hospital, Little Rock, AR 72206.

December 4—**Nutrition and Aging.** STAN. Thursday. 7 hrs.

December 5-7—**Human Sexuality.** Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

December 13—**Diagnosis and Treatment of Sleep Disorders Patients.** STAN at Marriott, Santa Clara. Saturday. 7 hrs. $35.

January 9-10—**New Concepts in Management of Chronic Pain.** Bay General Community Hospital at Half Moon Inn, Shelter Island, San Diego. Friday-Saturday. 10 hrs. $45. Contact: Karen Johnson, Bay Gen. Community Hosp., 435 H St., Chula Vista 92010. (714) 420-8182.

January 17—**The Virus of Love: Genital Herpes Infection.** UCLA. Saturday.

January 19-23—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday. 25 hrs. $290.

January 23—**Diagnosis and Treatment of Sleep Disorders Patients.** STAN at Marriott, Santa Clara. Friday. 7 hrs. $35.

January 25-31—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. One week. 50 hrs. Contact: Cont. Ed. in Health Sciences, UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

February 11-13—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Wednesday-Friday. 22 hrs. $275.

February 19-22—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Thursday-Sunday. 14 hrs.

February 23-27—**Basic Science for Clinicians.** STAN. Monday-Friday. 24 hrs. $290.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

September 18—**Left Brain Activity/Cognition—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

October 30—**Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

December 11—**Women, Violence and Sexuality—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatry Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

February 5—**Endorphins—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 19—**Right Brain Functioning—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

April 30—**Group Therapy—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

June 18—**Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

October 2-4—**Montana Medical Association Annual Meeting.** Thursday-Saturday. Bozeman. Contact: Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue. Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

EMERGENCY MEDICINE

October 3—**First Annual Poisoning and Toxicologic Emergencies Conference.** Portland. Friday. Red Lion/Lincoln Street. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 9-13—**Twelfth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

MEDICINE

November 13-14—**Symposium on Critical Care Medicine.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 23-25—**Northwest Review of Obstetrics & Gynecology.** Portland, Thursday-Saturday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

November 21—**Practical Applications of Ultrasound Scanning to Problems of Clinical Obstetrics.** Portland. Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education. University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

PSYCHIATRY

October 3-4—**Oregon Psychiatric Association 1980 Fall Meeting.** Portland. Friday-Saturday. Dammasch State Hospital. Contact: Veronica Story, Oregon Psychiatric Association, 5210 SW Corbett Ave., Portland, OR 97201.

OF INTEREST TO ALL PHYSICIANS

September 18-19—**Dermatology for the Non-Dermatologist.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

September 26—**Shaw Memorial Lectures on Geriatric Medicine.** Portland, Friday. Oregon Medical Association Build-

ing. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

October 3-4—**Washington State Medical Association Annual Meeting Scientific Program.** Vancouver, WA/Portland, OR. Friday-Saturday. Thunderbird-Jantzen Beach. Contact: Mrs. Marcia Wahlman, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA 98121. (206) 623-4801.

October 30-31—**Oregon Medical Association 106th Annual Scientific Assembly.** Hilton Hotel, Portland. Contact: Sondra Gleason, Oregon Medical Association, 5210 SW Corbett Avenue, Portland, OR 97201. (503) 226-1555.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

September 18-20—**Plastic Surgery for Primary MDs.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W School of Medicine.

September 19-20—**Spokane Developmental Disorders in Children.** Spokane. Friday-Saturday. Sacred Heart Hospital. Contact: U/W School of Medicine.

September 21-23—**Emergency Medicine in Office Practice.** Walla Walla. Sunday-Tuesday. Walla Walla General Hospital. Contact: Max W. Hammonds, MD, Director, Continuing Medical Education, Walla Walla General Hospital, 1025 South Second Avenue, P.O. Box 1398, Walla Walla, WA 99362. (509) 525-0480.

September 22-26—**Advances in Family Practice.** Seattle. Monday-Friday. U/W Health Sciences Building. Contact: U/W School of Medicine.

September 25-28—**The Spine, Advances in Practical Management.** Seattle. Thursday-Sunday. Olympic Hotel. Contact: U/W School of Medicine.

September 26-28—**Chest Conference.** Chelan, WA. Friday-Sunday. The Inn at Wapato Point, Lake Chelan. Contact: Lawrence Klock, MD, Chairman, CME, Washington Thoracic Society, 216 Broadway East, Seattle, WA 98102. (206) 322-7110.

September 27—**Annual Cancer Symposium: Current Concepts in Gynecological Malignancies.** Tacoma. Saturday. Tacoma General Hospital. Contact: Karen Tilley, Department of Oncology, Tacoma General Hospital, 315 South K Street, Tacoma, WA 98405. (206) 597-6964.

October 3-4—**Washington State Medical Association Annual Meeting Scientific Program.** Vancouver, WA/Portland, OR. Friday-Saturday. Thunderbird-Jantzen Beach. Contact: Mrs. Marcia Wahlman, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA 98121. (206) 623-4801.

October 8-10—**American College of Physicians: Modern Concepts in Allergy.** Seattle. Wednesday-Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

COURSE SPONSORS AND CONTACT INFORMATION

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Dept. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

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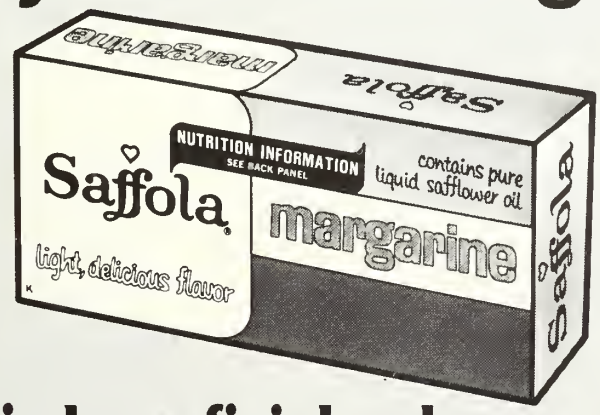

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October 18—**Lower Extremity Orthopedics in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Jackie Kersh, Office of Medical Education, Group Health Hospital, 201 16th Avenue East, Seattle, WA 98112, (206) 326-7348.

October 24-25—**Ophthalmology for Nurses and Office Assistants.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

November 6-9—**United States Section, International College of Surgeons Annual Meeting.** Las Vegas, NV. Thursday-Sunday. Aladdin Hotel. Contact: Franklin R. Smith, MD, 942 Medical & Dental Bldg., Seattle, WA 98101. (206) 682-1944.

November 13-15—**Street Drugs.** Seattle. Thursday-Saturday. Park Hilton Hotel. Contact: Marilyn Carlson, Northwest Hospital Education & Training Dept., 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ex. 686.

November 13-15—**Topics in Emergency Medicine.** Seattle. Thursday-Saturday. Seattle Hyatt House (Sea-Tac). Contact: Joan Palmer, c/o WSHA, 419 Occidental Avenue South, Seattle, WA 98104. (206) 624-7240.

November 14—**Annual Cancer Conference: Head and Neck Cancer.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

December 5—**Specialty Problems in Pediatrics.** Seattle, Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

January 23—**The Foot.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

February 6-7—**Workshops in Fluid and Electrolyte Disorders.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

February 27—**Diagnosis and Treatment of Common Arthritic Diseases.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 6-7—**Clinical Pharmacology for the Practitioner.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

April 4—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 1—**Management of Acute Medical Problems.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 15-16—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

June 5-6—**Pacific Northwest Chapter of the American College of Chest Physicians: Cardiopulmonary Symposium.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

July 25-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Saturday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

September 17, 1980

SPONSOR: Cottonwood Hospital
TITLE: **Tumor Conference**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

September 18-20

SPONSOR: University of Utah
TITLE: **Preceptor Teaching Skills**
LOCATION: Snowbird, Utah
FEE: $15.00
CREDIT: 10.5 hours
CONTACT: Donna Harris (801) 581-8250

September 22-25

SPONSOR: VA Regional Medical Education Center
TITLE: **Sexual Health**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: George Keiser, PhD (801) 582-1565, Ext. 1100

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UU: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

September 30-October 3
SPONSOR: University of Utah
TITLE: **Utah State Medical Association Scientific Meeting**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: Up to 12 hours
CONTACT: Maxcine Fry (801) 355-7477

October 1-2
SPONSOR: VA Regional Medical Education Center
TITLE: **Geriatric Assessment**
LOCATION: VAMC
FEE: To be announced
CREDIT: To be announced
CONTACT: Barbara Cordell, RN (801) 582-1565, Ext. 1100

October 3, 1980
SPONSOR: Cottonwood Hospital
TITLE: **Respiratory Distress**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

October 8, 1980
SPONSOR: Cottonwood Hospital
TITLE: **Tumor Conference**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

October 10-11
SPONSOR: University of Utah/The Upjohn Company
TITLE: **2nd Fall Arthritis Conference—Rheumatology: Clinical Assessment for the Practicing Physician**
LOCATION: Park City, Utah
FEE: $70.00
CREDIT: 11 hours
CONTACT: Mark Mueller, MD (801) 581-7724

October 16
SPONSOR: LDS Hospital (with Intermountain Thoracic Society, Utah Heart Association and University of Utah)
TITLE: **Postgraduate Course—Pulmonary Heart Disease**
LOCATION: LDSH
FEE: To be announced
CREDIT: 6 hours
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

October 22, 1980
SPONSOR: Cottonwood Hospital
TITLE: **Tumor Conference**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

November 6
SPONSOR: LDS Hospital
TITLE: **Pulmonary Heart Disease**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

December 12
SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Hypertension**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

January 24-31
SPONSOR: University of Utah
TITLE: **6th Annual Snowbird Radiology Conference**
LOCATION: Snowbird
FEE: To be announced
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8188

January 31-February 7
SPONSOR: University of California, San Francisco, CA
TITLE: **Infectious Diseases in Clinical Practice**
LOCATION: Park City, Utah
FEE: $200.00 ($250.00 after October 15, 1980)
CREDIT: 20 hours
CONTACT: Extended Programs in Medical Education
University of California
1308 3rd Avenue
San Francisco, CA 94143
(415) 666-2483 or 666-2894

February 9-12
SPONSOR: University of Utah
TITLE: **10th Annual Family Practice Refresher Course**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 28 hours
CONTACT: David N. Sundwall, MD (801) 581-8633

February 15-20
SPONSOR: University of Utah
TITLE: **Update on Clinical Microbiology and Immunology**
LOCATION: Park City
FEE: To be announced
CREDIT: 24 hours
CONTACT: John M. Matsen, MD (801) 581-5514

February 20-24
SPONSOR: University of Utah
TITLE: **26th Annual Postgrad Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: 16 hours
CONTACT: Theodore H. Stanley, MD (801) 581-6393

February 21-24
SPONSOR: University of Utah
TITLE: **OB-GYN 22nd Annual Postgrad Course**
LOCATION: Park City
FEE: To be announced
CREDIT: 16.5 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-27
SPONSOR: University of Utah/Intermountain Pediatric Society/American Academy of Pediatrics
TITLE: **Common Problems in Pediatrics III**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 16 hours
CONTACT: Bruce Buehler, MD (801) 581-7877

February 25-28
SPONSOR: University of Utah
TITLE: **Gynecologic Oncology Course**
LOCATION: To be announced
FEE: To be announced
CREDIT: 16.5 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-March 7
SPONSOR: University of Utah
TITLE: **Midwinter Radiology Pacific Cruise Meeting**
LOCATION: Departs from Los Angeles
FEE: $300.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

February 28-March 7
SPONSOR: University of Utah
TITLE: **6th Annual Advances in Internal Medicine**
LOCATION: Snowbird
FEE: $225.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1981—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 22-26, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 24-27, 1980, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 13-17, 1980, Pacific Beach Hotel, Waikiki.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1981—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 2-4, 1980, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Convention: November 7-8, 1980, Kachina Lodge, Taos.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 30-October 3, 1980, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 2-5, 1980, Thunderbird at Jantzen Beach, Vancouver, WA/Portland, OR.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Ramada Snow King Inn, Jackson.

February 28-March 7

SPONSOR: University of Utah
TITLE: **Nutrition and Contemporary Medicine**
LOCATION: Park City
FEE: $200.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 7-14

SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 14-21

SPONSOR: University of Utah
TITLE: **3rd Annual Park City Radiology Conference: Neuroradiology**
LOCATION: Park City
FEE: $240.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

April 8-10

SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ University of Arizona Center for Occupational Safety and Health/University of Texas Health Science Center, School of Public Health
TITLE: **3rd Annual Park City Environmental Health Conference: Legal and Ethical Dilemmas in Occupational Health**
LOCATION: Prospector Square Lodge, Park City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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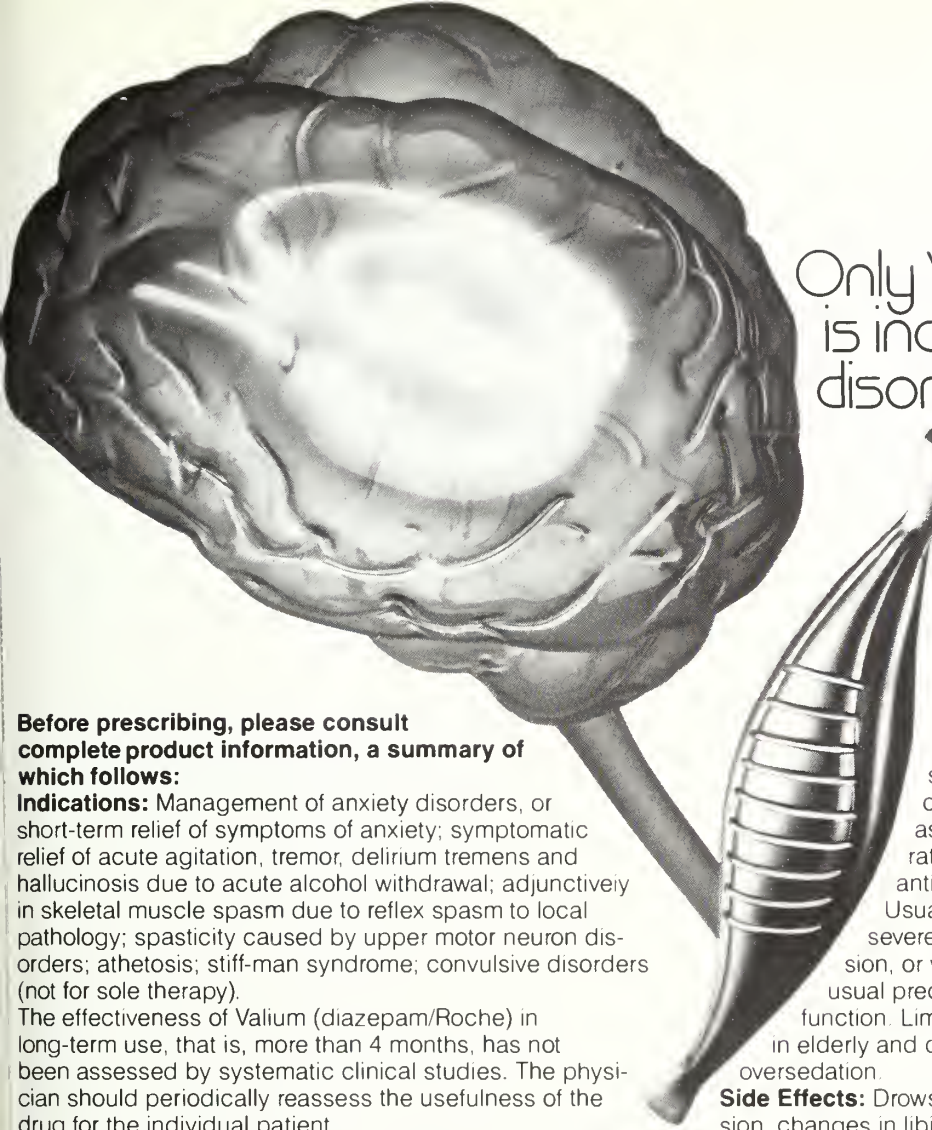

Only Valium® (diazepam/Roche) is indicated in anxiety disorders and as an adjunct in the relief of skeletal muscle spasm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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*The drugs studied included 7 commercially available and 2 investigational hypnotics.

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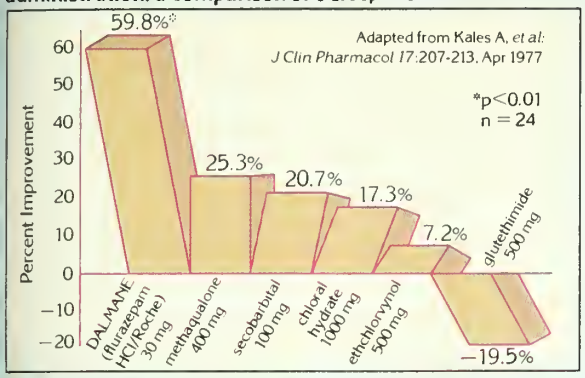

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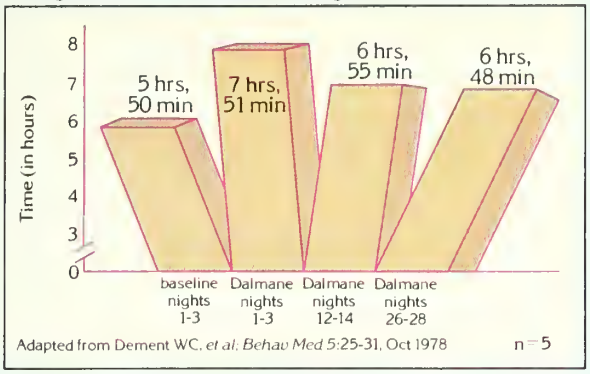

Improvement shown represents mean improvement, in hours, of total sleep time.

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REFERENCES:
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2. Dement WC, *et al: Behav Med 5*:25-31, Oct 1978
3. Kales A, *et al: Clin Pharmacol Ther 19*:576-583, May 1976
4. Frost JD Jr, De Lucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979

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- ☐ Consider other medications the patient may be taking (including alcoholic beverages) and be aware of possible drug interactions.
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- ☐ Monitor response to therapy and, based upon patient reassessment, determine need for continuing medication on an individual basis.
- ☐ Advise patients who ingest alcoholic beverages or other CNS depressants against doing so while on sleep medication. CNS stimulants such as caffeine should also be discontinued.
- ☐ Caution patients against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle shortly after ingesting the drug. In addition, as with all CNS depressants, patients may have reduced motor performance while on hypnotic therapy and should be advised accordingly.
- ☐ Avoid prescribing for suicidal or dependency-prone individuals whose histories indicate an inability to handle any psychoactive substances including alcohol.

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Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, e.g., excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
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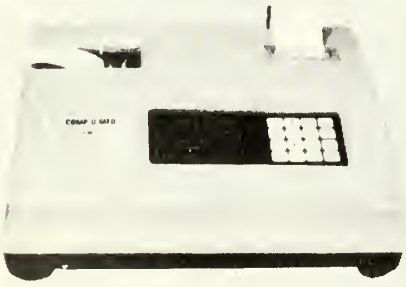

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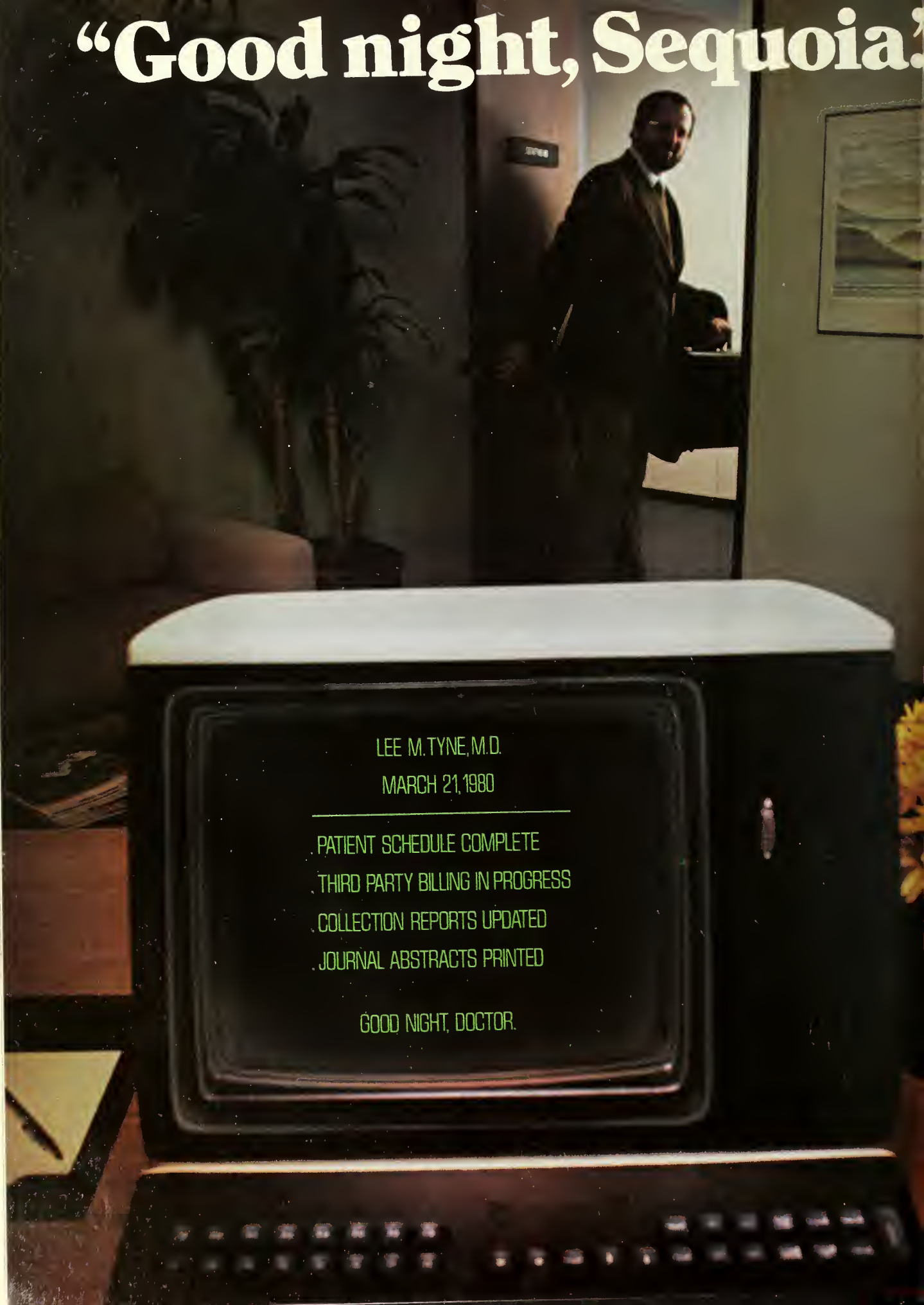

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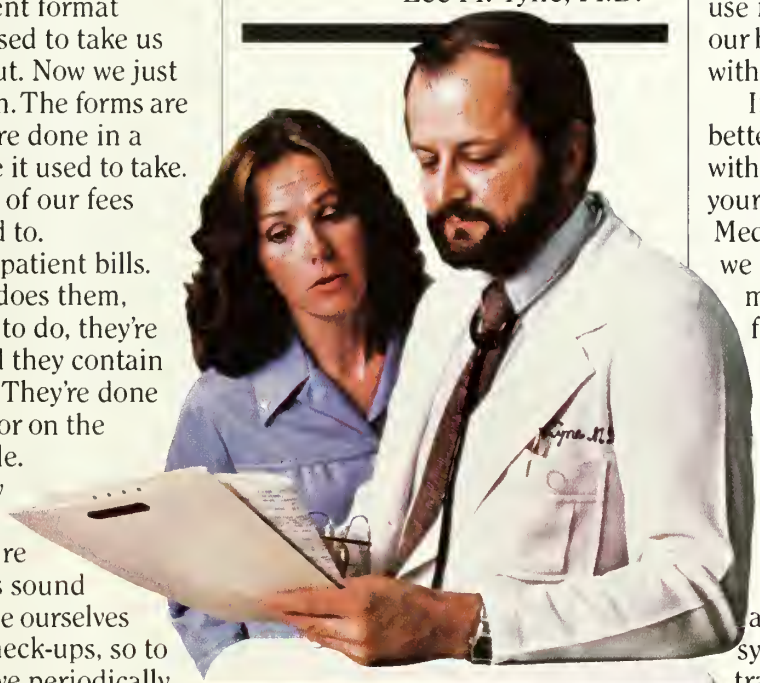

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CLINICAL CARDIOLOGY—Second Edition—Maurice Sokolow, MD, Professor of Medicine Emeritus, senior staff member, Cardiovascular Rssearch Institute; Formerly Chief of Cardiology and Program Director of the USPHS Clinical Cardiology Training Program, University of California, San Francisco; and Malcolm B. McIlroy, MD, Professor of Medicine, senior staff member, Cardiovascular Research Institute, University of California, San Francisco. Lange Medical Publicatons, Drawer L, Los Altos, California (94022), 1979. 718 pages, $17.50.

This well-written book encompasses virtually the entire field of adult clinical cardiology. It is the second edition, appearing a mere two years after the first. The authors state they have "incorporated clinically relevant aspects of many recent publications in the field of cardiology." They have "extensively revised" the chapters on pericardial disease and myocardial diseases. More space has been allotted to the "click-murmur" syndrome and to newer antiarrhythmia drugs. "Recommendations for antibiotic prophylaxis to prevent infectious endocarditis have been altered to conform to current American Heart Association guidelines."

The introductory chapters deal in admirable fashion with the anatomy and physiology of the circulatory system. There follows an excellent physiologic explanation of the common symptoms and signs of cardiac disorders. The two chapters on noninvasive and invasive studies are succinct in their description of basic principles involved in such investigations. Echocardiography and radionuclide cardiology studies are emphasized as procedures with both established clinical utility and a glowing future. Techniques which have faded from routine clinical practice, such as measurement of systolic time intervals, are properly only briefly mentioned.

Readers are referred elsewhere for details of noninvasive techniques such as the theory and practice of electrocardiographic interpretation. However, the chapters on conduction defects and cardiac arrhythmias are copiously illustrated with representative electrocardiograms and rhythm strips. Indeed the charts and illustrations throughout the book are of excellent quality. Of special importance are displays of echocardiographic and nuclear cardiology studies by the authors' colleagues at the University of California.

The chapters on common circulatory disorders encountered in North America show brilliant organization of a wealth of detail, with extensive references. Material in most chapters is remarkably current when one considers the breadth of the topics covered by two authors. The chapter on hypertension is particularly outstanding.

Certain controversial areas are dealt with in an arbitrary and sometimes cursory fashion. The conservative bias of the authors with regard to coronary artery bypass graft surgical operations is quite evident. The statement that "the length of time for which intra-aortic balloon pumping can be safely maintained is measured in hours rather than days" belies clinical experience.

The use of hypolipidemic drugs is described as "rational if lipid abnormalities are present." They do caution that the drugs should be given in small doses at first because side effects may be disturbing. The Coronary Drug Project's decision to drop dextrothyroxine from the study is not mentioned.

The discussion of the merits of anticoagulation in acute myocardial infarction focuses on venous thromboembolism, with insufficient consideration of the potential complication of cerebral embolism from mural thrombi in the left ventricle.

In the discussion of antiarrhythmia drugs, the complication of heart failure being precipitated by disopyramide is omitted. One searches in vain for any mention of digitalis toxicity being precipitated by quinidine therapy. Such omissions—of findings published very recently—are doubtless inevitable and underscore the importance of the authors' avowed policy of biennial revision.

Notwithstanding the above caveats, the book is a valuable text and is recommended for purchase by medical students and physicians in training.

ROBERT W. BURROUGHS, MD
Director, Echocardiography Laboratory
Deaconess Hospital
Spokane, Washington

* * *

ADVANCES IN HEART DISEASE—Volume 2—Edited by Dean T. Mason, MD, Professor of Medicine and Physiology; Chief, Cardiovascular Medicine, University of California, Davis, School of Medicine, and Sacramento Medical Center, Sacramento, CA—in the series: CLINICAL CARDIOLOGY MONOGRAPHS—Series Consultants: J. Willis Hurst, MD, and Dean T. Mason, MD, Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1978. 552 pages, $36.50.

If advances in cardiovascular diseases in recent years have been spectacular, their dissemination among the medical profession has grown exponentially. Each of the established journals dealing with cardiology or internal medicine now carries numerous review articles. Journals and regularly scheduled monographs devoted to "recent advances" have multiplied; furthermore, several review journals are now distributed free to the medical profession. In addition to this veritable flood of postgraduate-type of publications, many continuing education courses publish proceedings in book form. Dr. Mason's book is an outgrowth of his annual program and—judging from the fact that it is volume 2—is presumably meant to be another annual publication.

Of the 30 chapters, divided into eight sections, the author and his associates wrote 18. With the exception of the two-chapter section on "invasive evaluation," the authors' unit had input into all the sections. The book thus represents largely the perception of advances in cardiology by the cardiac unit of the University of California, Davis, School of Medicine.

Chapter 1, the introduction, presents a summary of the eight sections of the book, a *preview* of what is to come. Subjects covered range from new application of recognized diagnostic methods, discussion of newer techniques, pharmacological advances and cardiac rehabilitation. As is often the case in multiauthored books, the presentations are uneven, some appearing to be aimed at beginners, others at experienced cardiologists. The appearance of the book, the print and illustrations are carefully done, excellent in quality.

In general, the book is authoritatively and well written; one wonders, however, whether there is a need for more books, considering that the same information is available in a dozen of other places, often written by the same authors.

ARTHUR SELZER, MD
Pacific Medical Center
San Francisco

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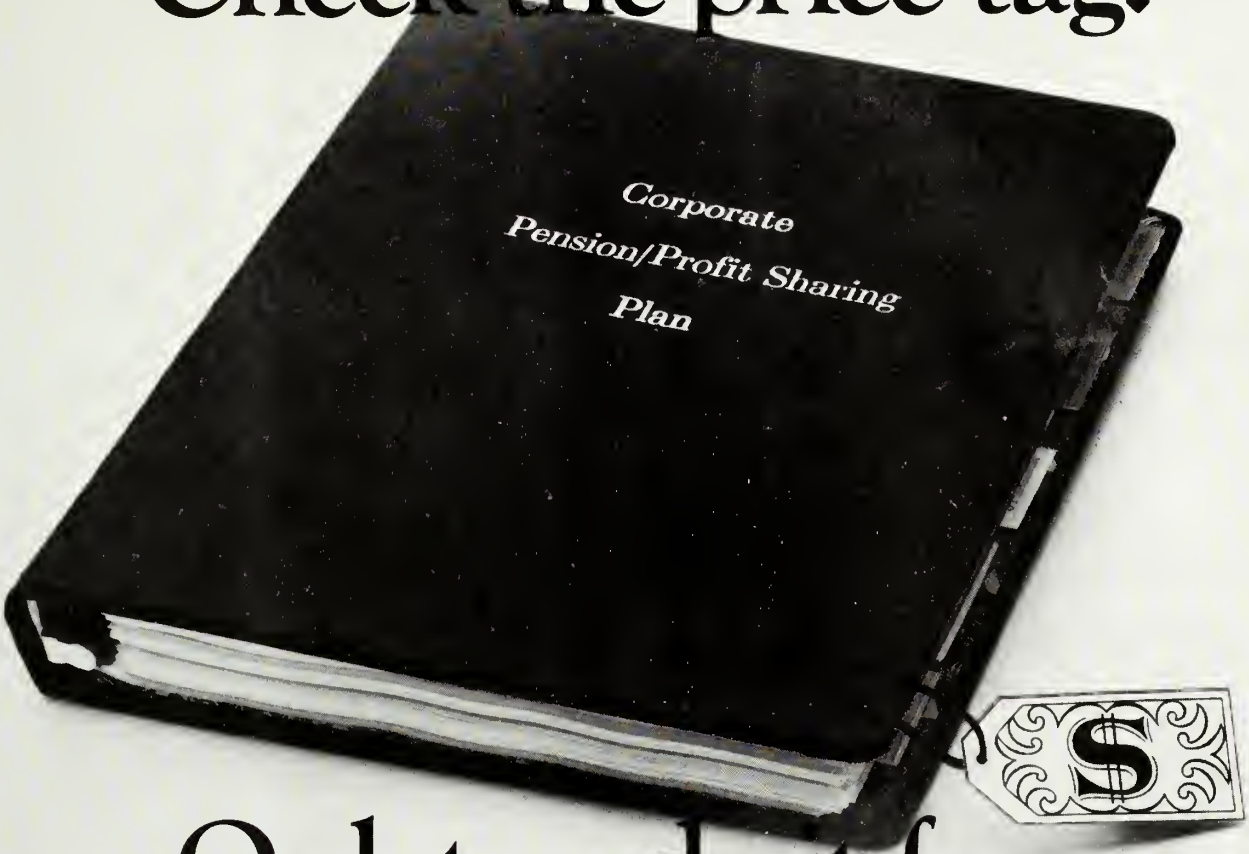

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The stress-secretion relationship in duodenal ulcer*

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*Librax has been evaluated as possibly effective for this indication.

Please see brief summary of prescribing information on last page of this advertisement.

1. Isenberg J, Richardson CT, Fordtran Pathogenesis of peptic ulcer, chap. 46 *Gastrointestinal Disease*, ed. 2, edited Sleisenger MH, Fordtran JS. Philade W.B. Saunders Company, 1978, vol. 1, pp. 800, 801.
2. Sun DCH: Etiology and pathology of ulcer, chap. 27, in *Gastroenterology*, ed edited by Bockus HL, *et al*. Philadelp W.B. Saunders Company, 1974, pp. 57

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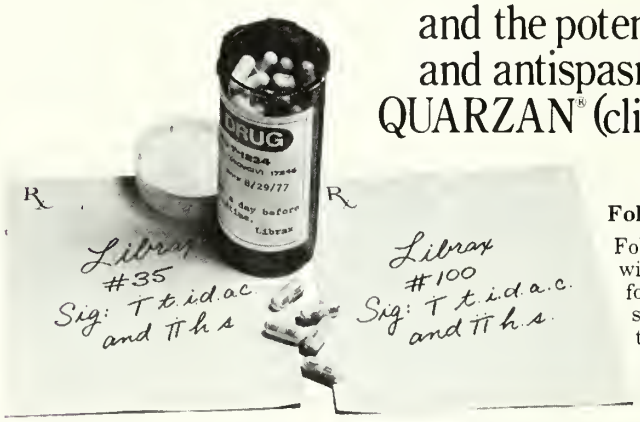

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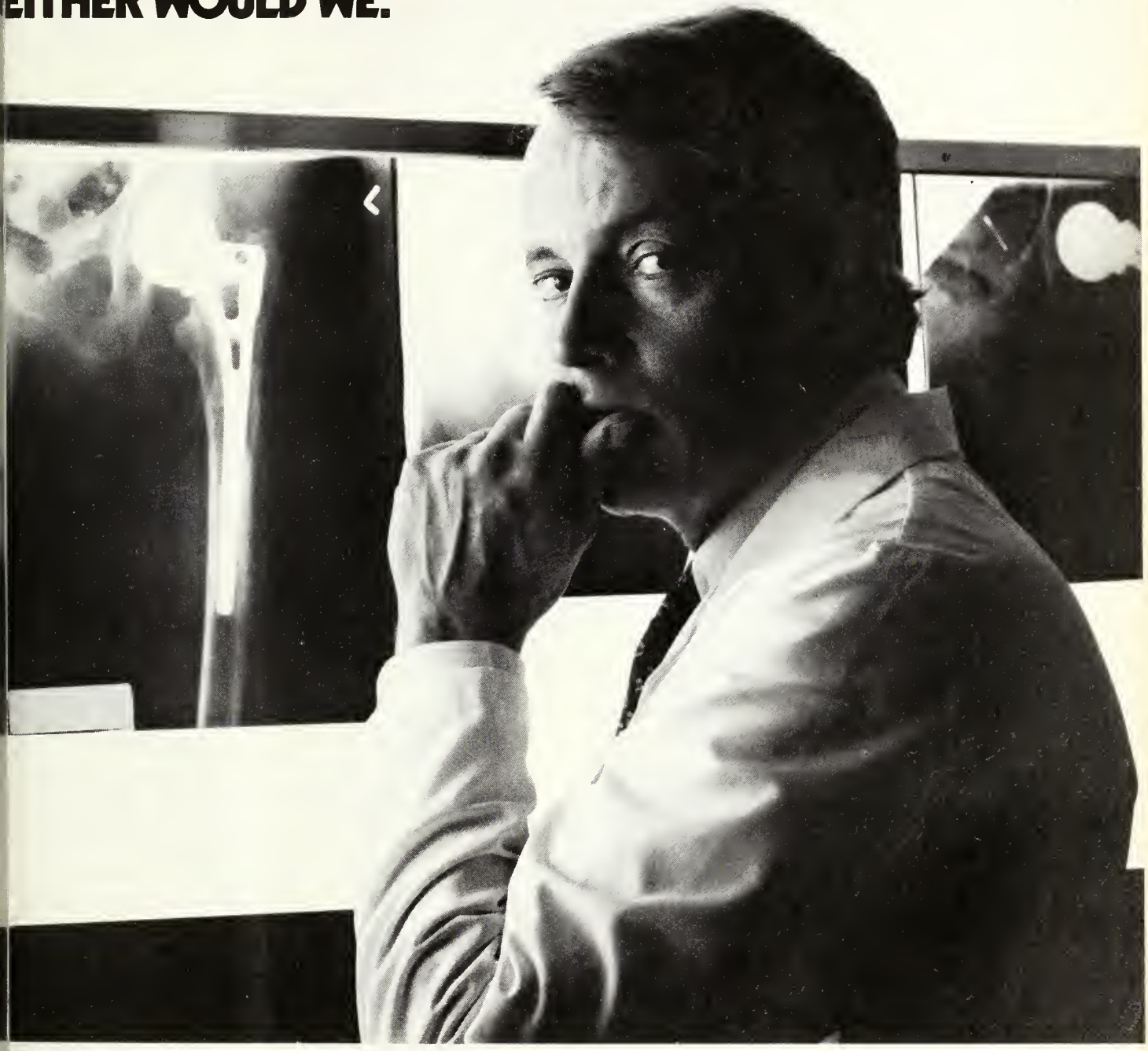

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Refer to: Brennan DC, Lewis JP: Remission-induction regimens in acute nonlymphocytic leukemia. West J Med 133: 279-288, Oct 1980

Remission-Induction Regimens in Acute Nonlymphocytic Leukemia

DONALD C. BRENNAN, MD, *and* JERRY P. LEWIS, MD, *Sacramento, California*

A sequential study was carried out involving 40 adults with acute nonlymphocytic leukemia (ANLL). The first 20 patients were treated with cytarabine (Ara-C) and 6-thioguanine (6-TG), the second 20 with a regimen that added a three-day course of daunomycin (DNM) to the Ara-C and 6-TG therapy. With both groups well matched for age, patients in the DNM-treated group had a higher complete remission (CR) rate but failed to survive longer than those in the Ara-C and 6-TG treatment group. In a comprehensive literature review of various treatments for adult ANLL, a higher CR rate but not significantly better survival for patients initially treated with DNM-combined regimens was found. Our analysis of cases and literature review suggest that while DNM is a very active drug, its use in the initial treatment of adult ANLL has not produced a significant improvement in overall survival or in survival of those brought into complete remission.

PROGRESS IN THE TREATMENT of acute nonlymphocytic leukemia (ANLL) in adults has advanced at a much slower rate than that of childhood acute lymphocytic leukemia (ALL). In the early 1960's survival of patients with untreated ANLL was only slightly improved by various single-agent therapies, including administration of methotrexate (MTX), 6-mercaptopurine (6-MP) or vincristine (VCR). These drugs gave a complete and partial remission (CR and PR) rate of 25 percent at best, with only a modest prolongation of median survival to four or five months.[1,2]

By the late 1960's the benefit of combination chemotherapy over single-agent treatment in some other malignant conditions, including acute lymphocytic leukemia, had been shown. Consequently, a variety of drug combinations evolved for the treatment of ANLL. One of the earliest of these was POMP (6-mercaptopurine, vincristine, methotrexate and prednisone). The largest study with this drug combination showed a CR rate of 25 percent in 66 patients.[2] Data on median survivals were not given; however, in a smaller series of patients treated with POMP the median survival was 193 days.[3]

The introduction of cytarabine (cytosine arabinoside; Ara-C) in 1964 provided clinicians for the first time with a highly effective drug for the treatment of ANLL.[4-8] Soon after its introduction this drug was being combined with a variety of other active drugs. One such combination, COAP (cyclophosphamide, vincristine, cytarabine and prednisone), yielded a 46 percent CR rate,[6] with a median survival for all patients of 245 days and a median survival for those who responded of 740

From the Section of Hematology and Oncology, Department of Medicine, and the Department of Pathology, University of California, Davis, School of Medicine, and the University of California Davis Medical Center, Sacramento.

This study was supported in part by the Max C. Fleischmann Foundation, Reno, Nevada.

Submitted November 14, 1979.

Reprint requests to: Jerry P. Lewis, MD, Chief, Section of Hematology and Oncology, Department of Medicine, 4301 X Street, Sacramento, CA 95817.

ABBREVIATIONS USED IN TEXT

ALL = acute lymphocytic leukemia
ANLL = acute nonlymphocytic leukemia
APL = acute promyelocytic leukemia
Ara-C = cytarabine (also cytosine arabinoside)
CR = complete remission
DNM = daunomycin
6-MP = 6-mercaptopurine
MTX = methotrexate
6-TG = 6-thioguanine
VCR = vincristine

days.[6,8] Subsequent investigators, using a modified COAP regimen in an older patient group, reported a CR rate of only 10 percent to 30 percent.[9,10] Nevertheless, in general, a combination of remission-induction drugs including Ara-C tended to yield better responses than those lacking this drug.

In 1969 Gee, Yu and Clarkson reported that administration of Ara-C and 6-TG every 24 hours yielded a 50 percent CR rate with a duration of maintained remission of approximately six months.[1] In this study, the median survival for all patients was 10.5 months and for those who responded, was approximately 23 months.[11] In 1972 Clarkson reported on their every-12-hour regimen, which in 43 patients gave a CR rate of 65 percent.[12] When these data were updated in 1975, the CR for 88 previously untreated patients was 56 percent; the median survival of all patients was a year, and the median survival of those who had a CR was 24 months.[11] In studies by Lewis and co-workers, reported in 1977, a similar regimen yielded a CR of only 41 percent.[13] Final analysis of these latter data showed a median survival for all patients of approximately a year and a median survival for those having a CR of slightly less than two years.

Heralded as a major advance in the treatment of ANLL was the introduction of anthracycline agents as antileukemia therapy. In the mid-1970's, several groups reported response rates of greater than 60 percent, using a three-day course of daunomycin (DNM; also daunorubicin) or doxorubicin (Adriamycin) plus Ara-C with or without other chemotherapeutic agents.[8,14-24] What has gone largely unnoticed, however, is that this higher rate of CR has not been associated with prolonged survival among those responding when compared with findings of earlier studies of Ara-C and 6-TG; of even greater importance are data indicating that even the median survival of all patients—those who responded as well as those who did not—has not improved with regimens that include anthracycline drugs.

This paper discusses these concerns and suggests that the use of anthracycline drugs should be reserved for those patients who are resistant to less toxic forms of therapy.

A retrospective review of 40 sequential cases of adult ANLL in previously untreated patients managed at the University of California Davis Medical Center (UCDMC), Sacramento, is presented. The first 20 were treated initially with Ara-C and 6-TG; the last 20 received, in addition to Ara-C and 6-TG, a three-day course of daunomycin. A review of reports published since the late 1960's concerning clinical trials of adult ANLL involving 15 or more patients is also presented. Our own clinical study and the literature review suggest that the incorporation of anthracycline drugs into initial induction regimens for previously untreated ANLL has not extended survival of patients with this disease.

Patients and Methods

Clinical Study

Hospital records of all adult patients with ANLL treated at the university medical center between September 1972 and December 1976 were reviewed. Forty previously untreated patients were seen during this time; drug therapy was begun and all cases were followed. Between September 1972 and November 1974, there were 20 patients (group 1) who were started on a regimen of Ara-C and 6-TG every 12 hours. They represent cases treated at our institution on Western Cancer Study Group (WCSG) Protocol 122. Details of this protocol, along with the remission-induction rates of the group-wide study, have already been reported.[13] This protocol was a randomized study of two induction regimens with Ara-C and 6-TG. Twelve patients in the study received 100 mg per m^2 of Ara-C and 80 mg per m^2 of body surface every 12 hours in five-day courses, while eight patients received these drugs every 12 hours until a remission in marrow was achieved or until the marrow cellularity had been reduced by 50 percent. The latter regimen was patterned after that of Clarkson.[12] As in the larger WCSG study, there was no difference between responses of our patients in the two subgroups. Therefore, for our purpose, we have combined the data on these 20 patients into our current group 1.

Patients in group 2 were treated between December 1974 and December 1976. These patients were treated with 1.5 mg of daunomycin per kg of body weight on the first three days in combination with 80 mg per m^2 of Ara-C and 6-TG, every 12 hours for seven days. Some of the patients also received 1.4 mg per m^2 (maximum 2 mg) of vincristine on days one and seven and 40 mg per m^2 of prednisone given orally each day for seven days. If a complete remission did not occur after recovery from marrow hypocellularity, the three- or five-drug regimens were repeated. The remission rate of the three- and five-drug regimens did not differ; therefore, these data were combined.

Once a CR was obtained in patients in either group, there were a variety of approaches to consolidation or maintenance treatment. Of the ten patients in group 1 who obtained a CR, eight received consolidation treatment with five-day courses of Ara-C and 6-TG in the same dosage schedule as used in induction, the course being given monthly for two or three months. Only one of these patients (CR of 11 months, survival of 27 months) went on to a more intensive maintenance therapy of the L-6 type,[11] which included vincristine, methotrexate, carmustine (BiCNU), 6-TG, cyclophosphamide, hydroxyurea and daunomycin. The remaining nine patients were not treated again until a relapse occurred. Consolidation treatment was not used in two patients in group 1 because of delayed recovery of marrow cellularity. Of the 13 patients in group 2 in whom a complete remission was achieved, five received consolidation therapy with Ara-C and 6-TG, with or without DNM, and two of these were placed subsequently on maintenance therapy, one with the L-6 type regimen (CR of 5 months, survival of 15 months), and one with monthly five-day courses of half doses of Ara-C and 6-TG (CR of six months, survival of 11 months). All patients were seen at monthly intervals and were retreated when relapse occurred.

All patients included in this study were on WCSG or UCDMC protocols and had given their informed consent. All protocols were approved by the university human subjects review committee.

Literature Review

A literature review was undertaken of clinical studies of 15 or more patients with ANLL. Abstracts were not included in this survey. The following data were sought: (1) number of patients, (2) drugs used to induce initial remission, (3) CR rate, (4) median duration of remission, (5) median survival of all patients and (6) median survival of those who achieved a CR.

The results of the literature review were organized in three series: series I consisted of data from patients treated with regimens that did not include either Ara-C and 6-TG in combination or anthracyclines, series II consisted of data on patients initially treated with Ara-C and 6-TG, and series III included all studies employing an anthracycline drug as an integral part of the first regimen to induce remission. Series IIIa contained studies in which the anthracycline agent was used alone or in combination with prednisone. Series IIIb contained all other studies using anthracycline drugs.

Statistics

When appropriate, data were analyzed statistically using the unpaired *t* test or chi-square test.[25]

TABLE 1.—*Results of Ara-C and 6-TG Regimen (Group 1) Compared With DNM, Ara-C and 6-TG Regimen (Group 2)*

	Number of Patients	*Age of Patients* (Years)*	*Number of CR's*	*Age of Patients With CR's* (Years)*	*Time to CR* (Months)*	*Duration of CR* (Months)*
Group 1	20	55.5	10	47	1.7	8.15
Group 2	20	55.5	13	33	1.1	5.6

	Survival of Patients With CR's (Months)*	*Number of PR's*	*Number of NR's*	*Age of Patients With NR**	*Survival of Patients With NR's* (Months)*	*Survival of Entire Group (Months)*
Group 1	25.6	3	7	67	2.6	11.6
Group 2	15.1	0	7	67	0.7	11.5

CR = complete remission; NR = no remission; PR = partial remission;
Ara-C = cytarabine (cytosine arabinoside); DNM = daunomycin; 6-TG = 6-thioguanine

*Median values.

Significance was considered to be important at the 0.05 level. Survival was plotted by the life-table method.

Results

The results of the clinical study are reported in Table 1. It is to be noted that the median age of patients in groups 1 and 2 was identical, 55.5 years. Not shown are the age ranges, which were similar. A CR was achieved in 50 percent of the patients in group 1 and in 65 percent of the patients in group 2. The median duration of CR in group 1 was 8.15 months, and the median duration of CR in group 2 was 5.6 months. Again, the difference is not significant; however, should a trend exist, group 1 patients appear to have the therapeutic advantage. With no patients in group 1 and only two patients in group 2 still alive, the median duration of survival for all patients and for those who achieved a CR are as follows: group 1, 11.6 and 25.6 months, and group 2, 11.5 and 15.1 months, respectively. Again, there is no significant difference between these statistics; however, were there to be a trend, as before, the trend for longer survival favors patients in group 1. The length of survival of all patients is displayed in Figure 1. The median time from start of treatment to CR in group 1 was 1.7 months and in group 2 was 1.1 months. The ranges were 1.3 to 4.4 and 0.7 to 2.1 months, respectively. This difference is significant at $P = < 0.05$.

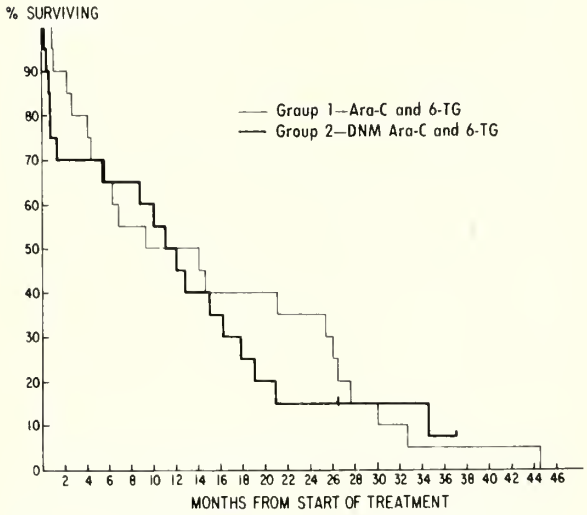

Figure 1.—Survival curves of patients studied at the University of California Davis Medical Center, Sacramento. The two upright marks indicate the location in time of the two surviving patients. (Ara-C = cytarabine; DNM = daunomycin; 6-TG = 6-thioguanine)

Table 2 shows the number of hospital days, units of packed red blood cells, platelet concentrates and days of systemic antibiotic drug therapy for those patients in whom a CR was achieved in the two groups. Because of the small number of patients, only the number of platelet

TABLE 2.—*Support Care During Induction Therapy in Groups 1 and 2**

	In Hospital	*Granulocyte Count <500/cu mm*	*Systemic Antibiotic Therapy*	*Platelets <20,000/ cu mm*	*Platelet Units Transfused*†	*RBC Units Transfused*
Group 1	36 (15-57)	10 (7-41)	11 (0-27)	11 (0-32)	30 (0-95)	11 (0-18)
Group 2	29 (21-54)	17 (8-39)	19 (10-27)	14 (10-23)	96 (20-130)	10 (4-52)

*All values are medians with ranges of values in parentheses, and refer to number of days unless otherwise specified.
†Significant at <0.05.

TABLE 3.—*Days of Survival Time Spent in Hospital by Those With Complete Response Who Have Died*

Group 1			*Group 2*		
Patient	*In Hospital/Survival* (Days)*	*Percent*	*Patient*	*In Hospital/Survival*† (Days)*	*Percent*
1	82/918	8.9	1	38/391	9.7
2	81/771	10.5	2	176/1059	16.6
3	94/793	11.9	3	97/540	18.0
4	215/994	21.6	4	115/638	18.0
5	172/787	21.9	5	65/245	26.5
6	94/426	22.5	6	111/316	35.1
7	187/643	29.1	7	62/167	37.1
8	131/443	29.6	8	174/458	38.0
9	316/838	37.7	9	142/361	39.3
			10	134/335	40.0

*Median—21.9 percent; mean—21.5 percent.
†Median—30.8 percent; mean—27.1 percent.

units transfused differed between groups 1 and 2 at the $P = < 0.05$ level.

Table 3 concerns only those with complete responses who have died, and it is apparent that most such patients spent a high percentage of their survival time in the hospital. Although group 2 patients spent fewer days in the hospital until their first CR than did those in group 1, these patients tended to spend a greater percentage of overall time in the hospital than did patients in group 1.

Table 4 lists the results of the literature survey on ANLL treatment studies.

Discussion

Progress in the treatment of acute lymphocytic leukemia has been impressive. Over the past decade there has also been steady improvement in CR rates, from 25 percent to greater than 50 percent for patients with ANLL. It is generally assumed that this doubling of CR in ANLL is associated with a comparable improvement in median duration of CR, median survival of responders and overall median survival of treated patients. Our clinical studies suggest that such is not the case, and these conclusions are confirmed by a comprehensive review of the literature.

In our clinical studies a possible bias would have been introduced if group 1 consisted of patients with favorable features and group 2 consisted of patients with less favorable features. The most important prognosticator of response is age, with older patients having a significantly worse prognosis than younger ones.[13,26] In our study, both groups had the same median age and had comparable numbers of patients older than 50. As in other studies, our older patients were indeed less likely to achieve a CR. In only 4 of 12 patients older than 50 in group 1, and 5 of 11 patients more than 50 years old in group 2, CR was achieved. Combining the two groups, complete remission was achived in 1 of 5 patients (20 percent) in the eighth decade, 4 of 11 patients (36 percent) in the seventh decade, and 4 of 7 patients (57 percent) in the sixth decade. In contrast, in the 16- to 40-year age group (again considering both groups together) CR occurred in 10 of 11 patients (91 percent) and, if the age group is extended to patients 16 to 50 years old, the CR rate was still high at 82 percent (14 of 17 patients).

Subtypes of leukemia could have affected our results. However, there were no cases of acute monocytic leukemia or erythroleukemia in either of our two groups, and although there were four patients in group 2 with acute myelomonocytic leukemia, compared with two in group 1, this subtype of adult ANLL has not been shown to have any better or worse prognosis than the other subtypes of ANLL.[11,26] Another subtype of ANLL is acute promyelocytic leukemia (APL), characterized by a predominance of promyelocytes rather than myeloblasts in the marrow and accompanied by at least laboratory, if not clinical, evidence of disseminated intravascular coagulation (DIC). Because of DIC, these patients with APL are often at greater risk for early death due to hemorrhage.[27-29] However, there are also data indicating that APL may be even more responsive than other subtypes of ANLL to chemotherapy, in particular to daunomycin.[27,29] Thus, the two patients with APL in group 1 not receiving DNM may have been at a disadvantage, while the four patients with APL in group 2 receiving DNM may have had a greater chance for prolonged survival. However, of the six patients with APL, the only instance of early death was in group 2 (survival of 1.3 months), while the two patients with APL in group 1 had relatively good survival times of 21 and 26 months. One of the APL patients in group 2 has had the longest duration of CR, still being in her first complete remission, 32.5 months after it was achieved.

Numerous other prognostic factors at the time of initial presentation of ANLL have been identified by others.[26] These include active infection, platelet count, absolute granulocyte count, absolute peripheral blood blast count and hemoglobin; each has been examined for possible prognostic significance, with varying degrees of success.[26] Patients in groups 1 and 2 did not differ with respect to these potential prognostic factors.

Some studies have suggested that granulocyte transfusions may enhance survival of the patient with documented infection and granulocytopenia.[30-33] Because granulocyte support was used liberally in the care of group 2 patients and only rarely in the care of group 1 patients, any such benefit would have favored those in group 2.

Of the ten patients with complete response initially to Ara-C and 6-TG induction treatment, eight were retreated with Ara-C and 6-TG on relapse, five had a second complete remission (lasting 1.8, 2.0, 3.0, 3.8 and 5.8 months) and three had a partial remission (lasting 3.0, 4.0 and 9.7 months). The other two patients in group 1 were treated with daunomycin, Ara-C and 6-TG

TABLE 4.—*Summary of Data Collected From Literature Review*

Regimen	No. of Patients	CR (Percent)	Duration of CR (Days)	Median Survival of All Patients (Days)	Median Survival of Patients With CR's (Days)
Series I					
Regimens Not Using Ara-C Plus 6-TG or DNM					
1. POMP[2]	66	25	..	..	..
2. POMP[3]	39	44	..	193	..
3. POMP[35]	51	26	..	..	..
4. POMP[36]	21	28	61	..	334
5. Ara-C[6]	51	31	322	56	560
6. Ara-C[5]	113	32	406	28	..
7. Ara-C[37]	49	14	140	45	320
8. Ara-C[7]	36	25	270	50	325
9. Ara-C, HU[38]	32	44	..	..	..
10. Ara-C, CTX[39]	29	31	242	..	272
11. CTX, Ara-C, Pred[9]	31	10	..	..	..
12. CTX, Ara-C, Pred[10]	25	28	74	152	..
13. CTX, Ara-C, Pred, L-A[10]	27	33	284	23	..
14. CTX, Ara-C, O[40,41]	52	44	..	180	790
15. CTX, Ara-C, MTX[42]	50	28	..	..	..
16. Ara-C, O, Pred[8,43]	175	54	248	75	..
17. Ara-C, O, Pred[8]	89	43	270	52	..
18. Ara-C, O, Pred[44]	41	44	581	56	..
19. COAP[45]	39	44	294	77	..
20. COAP[6,8]	57	46	427	245	740
21. COAP[8]	94	44	270	45	..
22. Ara-C, 6-MP[46]	17	35	>150	130	>285
Total	1,184	..	..	..	..
Median	..	33	270	56	330
(Range)	..	(10-54)	(61-581)	(28-245)	(272-790)
Series II					
Ara-C Plus 6-TG					
23. Ara-C, 6-TG[1,12]	38	50	182	320	700
24. Ara-C, 6-TG[42]	48	25	..	..	..
25. Ara-C, 6-TG[37]	66	36	266	130	455
26. Ara-C, 6-TG[12]	88	56	300	365	730
27. Ara-C, 6-TG[47]	136	37	..	..	..
28. Ara-C, 6-TG[48]	150	44	c.240	..	..
29. Ara-C, 6-TG[13]	81	41	308	..	511
30. AAFC, 6-TG[49]	50	50	..	..	..
Total	657	..	..	..	..
Median	..	42.5	266	320	605
(Range)	..	(25-56)	(182-308)	(130-360)	(455-730)
Series IIIa					
DNM Alone or With Prednisone					
31. DNM[36]	22	50	63	..	365
32. DNM[50]	33	49	205	353	419
33. DNM[51]	36	56	..	..	..
34. DNM[52]	82	17	..	..	..
35. DNM[52]	39	43	..	..	..
36. DNM, Pred[53]	45	27	180	182	395
Total	257	..	..	..	..
Median	..	46	180	268	395
(Range)	..	(17-56)	(63-205)	(182-353)	(365-419)

Series IIIb

DNM Plus Other Drugs

Regimen	No. of Patients	CR (Percent)	Duration of CR (Days)	Median Survival of All Patients (Days)	Median Survival of Patients With CR's (Days)
37. DNM, Ara-C±L-A[54]	23	61	..	..	..
38. DNM, Ara-C[55]	24	50	..	..	..
39. DNM, Ara-C[56]	255	47	..	..	..
40. DNM, Ara-C[57]	19	53	..	240	..
41. DNM, Ara-C[58]	191	33	126	..	404<536
42. DNM, Ara-C[59,60]	81	46	210	..	441<455
43. DNM, Ara-C[61-64]	139	38	191	..	270
			305	..	510
44. DNM, Ara-C[65]	148	52	231	..	431
45. DNM, Ara-C[16]	86	65	..	..	..
46. DNM, Ara-C[66]	52	58	167	..	..
47. DNM, Ara-C[67]	40	75	..	..	..
48. DNM, Ara-C[66]	37	60	..	..	..
49. DNM, Ara-C[20]	15	67	..	..	..
50. DNM, Ara-C[22]	19	63	..	..	..
51. DNM, Ara-C[18]	16	69	..	..	..
52. DNM, Ara-C[19]	23	65	..	..	..
53. DNM, Ara-C[68]	17	47	455	..	..
54. DNM, Ara-C[23]	52	60	..	..	..
55. DNM, Ara-C[69]	30	53	365	395	..
56. DNM, Ara-C,±Le[24]	60	60	174	255	..
57. DNM, Ara-C, O[70]	23	48	..	..	..
58. DNM, Ara-C, O, Pred[8]	89	39	322	82	..
59. Adria, Ara-C, VP[79]	31	48	..	..	..
60. Adria, Ara-C, O, Pred[80]	325	65	..	301	546
61. Adria, Ara-C[81]	21	57	..	..	..
62. Adria, Ara-C[21]	30	70	336	..	..
63. DNM, Ara-C, 6-TG[47]	148	41	..	..	..
64. DNM, Ara-C, 6-TG[71]	61	49	..	..	..
65. DNM, Ara-C, 6-TG[48]	150	49	c.150	..	..
66. DNM, Ara-C, 6-TG[72,73]	41	61	255	..	..
67. DNM, Ara-C, 6-TG[23]	122	48	..	..	..
68. DNM, Ara-C, 6-TG[74]	30	47	140	175	525
69. DNM, Ara-C, 6-TG[75]	20	85	336	490	..
70. DNM, Ara-C, 6-TG[14]	28	79	280	..	375
71. DNM, Ara-C, 6-TG, Py[50]	33	46	168	157	383
72. DNM, Ara-C, 6-TG, Pred+COAP+POMP[76]	25	60	462	..	714
73. DNM, Ara-C, 6-TG, Adria, CTX[77]	62	48	210	..	395
74. DNM, Ara-C, 6-TG, O, Pred[15]	121	66	..	..	..
75. DNM, Ara-C, 6-MP, O, Pred[78]	77	35	152	c.180	395
76. DNM, Ara-C, 6-MP, MG, Pred[66]	21	52	290	..	..
77. DNM, Ara-C, 6-MP, Pred[82]	32	81	371	378	..
78. DNM, Ara-C, 6-TG[83]	43	56	224	252	532
79. DNM, Ara-C, 6-MP, Pred[84]	37	62	330	309	510
80. DNM, Ara-C, VCR, Pred[85]	54	35	315	77	..
Total	2,951	..	..	..	..
Median	..	54.5	255	252	436
(Range)	..	(33-85)	(126-462)	(77-490)	(270-714)

AAFC = anhydrocerabinosyl-fluorocytosine Adria = Adriamycin (doxorubicin)
Ara-C = cytosine arabinoside (cytarabine) COAP = (cyclophosphamide, vincristine, Ara-C and prednisone)
CR = complete remission CTX = Cytoxan (cyclophosphamide) DNM = daunomycin (also daunorubicin)
HU = hydroxyurea L-A = L-asparaginase Le = levamisole MG = methylglyoxal bis guanylhydraxone
6-MP = 6-mercaptopurine MTX = methrotrexate O = Oncovin (vincristine)
POMP = (6-mercaptopurine, vincristine, methotrexate and prednisone) Pred = prednisone
Py = pyrimethamine 6-TG = 6-thioguanine VCR = vincristine VP = VP 16-213

at relapse, one having a CR of 30 months and the other showing no response. DNM alone or with Ara-C and 6-TG was also given to four other patients in their second relapse from CR's following Ara-C and 6-TG therapy; two of these patients had yet a third CR of 1.2 and 2.0 months, and extended survival times of 2.6 and 9.0 months, respectively, from the start of DNM treatment.

Of the 13 patients with an initial complete response to DNM, Ara-C and 6-TG treatment, 12 have had relapses; 11 of these 12 patients were treated again with the same three drugs and 8 had a second CR (lasting 1.4, 2.0, 3.5+, 3.6, 4.0, 4.4, 5.5 and 6.8 months). Of the three other patients, one had no response and two had partial remissions lasting 1.0 and 4.0 months. One of the patients with a partial remission subsequently responded to single-agent DNM therapy; the other had a CR following treatment with 5-azacytidine.

Although the number of patients involved is small, it appears that those in group 1 not only have a good chance for a modestly long response to the initial Ara-C and 6-TG treatment but, based on studies of Greenberg and co-workers,[34] they also seem to have good backup treatment with an anthracycline drug. The group 2 patients had fewer second-line treatments available once they failed to respond to an anthracycline drug.

Besides providing a better CR rate, it is hoped that any apparent advance in treatment would also produce a more prolonged duration of the complete remission. Again, the DNM regimen fell short of our expectations. The 13 patients with complete response in group 2 had a median duration of CR of only 5.6 months (mean 7.5+ months, range 2.1 to 32.4+ months); those who had a response in group 1 (ten patients) had a median duration of CR of 8.15 months (mean 9.0 months and range 3.1 to 18.0 months).

Because criteria for admittance to hospi al and for erythrocyte, platelet and antibiotic support treatment were similar throughout the four years of this study, we hoped these measurements would aid in the comparison of toxicity of the two regimens. As expected and shown in Table 2, patients on both regimens required considerable transfusion and antibiotic support. The only statistically significant difference between the two regimens, with reference to these potential determinants of toxicity, was in platelet transfusions, with group 1 patients with complete response receiving a median of 30 units of platelets during induction therapy, while group 2 patients with complete response received a median of 96 units of platelets. This difference may be due, at least in part, to the fact that patients in group 1 were treated at a time when platelet tranfusions were not used as frequently as they are now, because the number of days of platelet counts falling below 20,000 per cu mm during induction therapy for complete responders were similar in both groups.

Five of the 20 patients in group 2 died within a month of the start of treatment, compared with only 1 of the 20 patients in group 1. Yet the status of these five patients at presentation was no different from that of the other patients with ANLL, except for the one 79-year-old patient who had a fever and lung infiltrate and died a few days after starting chemotherapy. The other four patients who suffered early deaths presented with no fever; three of the four had platelet counts above 50,000 per cu mm and three of the four had absolute granulocyte counts below 1,000 per cu mm. What is common to these five patients is their advanced age, all being 64 years of age or older.

Conclusions

From this retrospective review of patients treated at our facility, we are unable to support the thesis that the early use of daunomycin in patients with ANLL represents a major advance. DNM therapy may yield a higher rate of complete remission, but it does not appear to prolonge life. Unfortunately, DNM therapy is also associated with a higher rate of early deaths and there exists no advantage in overall median survival of all patients so treated. In the last analysis, this must be the single most important criterion to measure the value of a given induction regimen, now that 50 percent or more of patients are entering a CR.

Our comprehensive literature review supports the conclusions of our clinical study. In this survey, we found over 70 studies on the treatment of adult ANLL (Table 4). Factors influencing results of treatment, such as differing median age of the patient population, inclusion of patients with adult acute lymphocytic leukemia in the reported results, and use of differing doses and schedules of the same drugs in different studies, make it difficult to rigorously compare various treatment regimens simply from the CR and survival data listed in Table 4. However, some general comments can be made about these past studies.

Studies involving Ara-C alone or DNM alone are interesting in that although they do show

daunomycin to be the best single agent for inducing a CR (17 percent to 56 percent range compared with 14 percent to 32 percent for Ara-C alone), the duration of CR tended to be shorter in patients receiving DNM alone (Table 4, numbers 31 through 36) than for those receiving Ara-C alone (Table 4, numbers 5 through 8). The overall length of survival of those in whom CR was achieved with Ara-C ranged widely but probably was comparable to the survival of those in whom CR occurred with DNM therapy.

Series II in Table 4 lists all the studies using Ara-C and 6-TG in combination. In study 23 and study 25 an every-24-hour schedule for Ara-C and 6-TG was used, while in the other studies an every-12-hour schedule was carried out as was the case for our patients. The results of therapy for our 20 patients (Table 1) are comparable to those of the larger trials reported in the literature.

As in our study, the literature review seems to show that although the Ara-C plus 6-TG studies have a lower CR rate (25 percent to 56 percent range) than the numerous DNM combination studies (many in the 60 percent to 70 percent range), the CR duration and survival data do not show any clear-cut superiority for the DNM combinations. The median survival of CR patients receiving DNM plus Ara-C is 436 days, with the best result being 714 days (study 72). These data are no better than those for Ara-C and 6-TG therapy.

This literature review did not try to answer the question of whether it is necessary to introduce an anthracycline drug early in the treatment of patients with acute promyelocytic leukemia[27,29] or in patients 60 years old or older.[86] If certain subgroups can be shown to benefit from early administration of anthracycline agents, it is likely that other subgroups will be shown to be harmed by this approach. Pending confirmation of subgroups that benefit from the early introduction of DNM, we do not find from our own experience or from that reported in the literature any solid justification for the general impression that early inclusion of DNM or doxorubicin (Adriamycin) into induction-remission regimens for adult ANLL is advantageous. Therefore, we conclude that in treating adults with ANLL, anthracycline drugs should be withheld until resistance to Ara-C and 6-TG can be shown or until it is confirmed that selected subgroups of patients with ANLL benefit from the early introduction of these agents.

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Attitudes Toward Weight Gain in Pregnancy

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Recently, there has been increased interest in the influence of maternal prenatal nutrition on the course and outcome of pregnancy. Evidence has accumulated that a woman's weight before pregnancy and the weight gained during pregnancy directly affect infant birth weight, incidence of neonatal mortality, and growth and development of the infant during the first year of life. Although recent recommendations for weight gain in pregnancy have been liberalized, a survey of 195 pregnant women who had prenatal visits in both clinic and private offices showed deficiencies in their understanding of the subject. Some 37 percent of women believed they should gain 20 pounds (9 kg) or less during pregnancy. Eight percent admitted to dieting before at least one antenatal visit and 54 percent thought their doctor would not be concerned about too little weight gained during pregnancy. This suggests that many women and some doctors are still ignorant of current concepts of proper nutrition during pregnancy. Apparently, increased lay and professional educational efforts are needed.

HISTORICALLY, WEIGHT RESTRICTION for women during pregnancy has been advocated, based on findings that showed a relationship between high weight gain and a host of obstetric and neonatal problems. Since the turn of the century, the threat of delivering a large baby has been greatly reduced due to improvements in operative obstetric procedures, and attempts to "grow the baby to fit the pelvis" have been generally abandoned. Prevention of toxemia of pregnancy became the next chief reason for limiting weight gain, and there began an era of stringent dietary restriction, especially of protein, that extended into the 1950's and even to some degree to the present.[1] More recently, it has been concluded that there is no evidence that prescribed caloric restrictions during pregnancy has any effect on the incidence of toxemia.[2]

What is the optimal, ideal or physiological total weight that should be gained during pregnancy? No single figure exists that can be regarded as *normal.* Numerous large studies confirm that the average total weight gain in a "normal" pregnancy is about 24 pounds (10.8 kg), with a standard deviation of about 10 pounds (4.5 kg). Reported mean figures of total weight gain in women who were

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allowed to eat to satisfy their appetites are in the range of 22 to 27 pounds (10 to 12 kg).[3]

It has been consistently shown that after gestational age, maternal weight before pregnancy and weight gained during pregnancy play the greatest role in determining an infant's birth size and incidence of neonatal mortality.[1,4] The positive correlation between birth weight and mother's weight gain during pregnancy holds when numerous other factors are introduced into the analysis, including maternal height, weight before pregnancy, length of gestation,[5] cigarette smoking, race and socioeconomic status.[6]

More important, results from the collaborative study by the National Institute of Neurological Diseases and Stroke[7] found that the greater the mother's weight gain, the better an infant's growth and performance during the first year of life. This analysis suggests that birth weight may be the critical intervening variable between maternal weight gain and infant growth and performance.

The purpose of the present study is to determine the attitudes of pregnant women toward dieting during pregnancy and weight gain during pregnancy. An attempt was made also to elicit impressions of pregnant women regarding their physicians' preference concerning weight gain.

Patients and Methods

The survey involved asking 195 pregnant women to fill out a questionnaire designed to establish attitudes toward weight gain in pregnancy. Of these, 99 women were interviewed at the antepartum clinic at the Cedars-Sinai Medical Center in Los Angeles, and 96 were interviewed in the Beverly Hills office of a private group of obstetricians on the attending staff of Cedars-Sinai Medical Center.

Results

No significant differences were noted between responses of clinic and private patients. Responses indicate that 37 percent of patients believed that they should gain 20 pounds (9 kg) or less during pregnancy (Table 1). On the opposite end of the scale, 4 percent of the women believed that they should gain more than 30 pounds (13.5 kg) during pregnancy, and 8 percent admitted to dieting before at least one antenatal visit. Although not defining the terms "too little weight gain," and "too much weight gain," it is clear that many more patients thought their doctor would be concerned with too much weight gain (88 percent of patients) rather than too little (39 percent of patients).

TABLE 1.—*Survey Questions Asked of 195 Pregnant Women Regarding Weight Gain During Pregnancy*

Question	*Response (Percent)*
How much weight do you think you should gain during this pregnancy?	
• should lose weight	2
• 0-10 pounds	5
• 11-20 pounds	30
• 21-30 pounds	52
• 31-40 pounds	3
• over 40 pounds	1
• I am not concerned with how much weight I gain	2
• no answer	5
Do you ever diet immediately before your doctor's office visit?	
• yes	8
• no	91
• no answer	2
Do you feel that your doctor would be upset by too little weight gain?	
• yes	39
• no	54
• no answer	6
Do you feel that your doctor would be upset by too much weight gain?	
• yes	88
• no	7
• no answer	5

Discussion

Current recommendations are for women of normal weight to gain an average of at least 22 to 27 pounds (10 to 12 kg) during pregnancy.[8] Obese patients may not need to gain as much, but they should not be on reducing diets during pregnancy.[2] Once excessive weight gain has occurred, there is no going back. All that can be accomplished from that time forward is to encourage a more moderate pattern of weight gain. Ketogenic diets, such as the Atkins diet or other protein-sparing diets, are particularly contraindicated because ketosis may damage the fetus.[9]

Our study has shown that in a selected group of pregnant patients, there were substantial deficiencies in understanding of nutritional guidelines and weight gain in pregnancy. Differences between clinic and private patients were minor. Frequently, obstetricians play the key role in determining dietary practices in pregnancy. A survey published in September 1978[10] suggested that many physicians caring for obstetric patients are deficient in two areas: in their knowledge of proper nutritional

requirements during pregnancy and in counseling their patients concerning nutrition.

A 1970 National Academy of Sciences report[2] emphasizes the need to abandon therapeutic restrictions of caloric intake during pregnancy and suggests the need to return to positive prenatal diet counseling, that is, emphasis on the nutritional requirements of pregnancy and the food intake needed to supply these nutrients. From a clinical perspective, in light of consistent animal data[11] and inconclusive but supportive human data,[11,12] it seems reasonable to concentrate on the quality of nutritional intake during pregnancy rather than on the quantity.

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Protection of a Newborn Infant of a Tuberculous Mother

WHAT IS THE BEST WAY to protect a newborn infant of a tuberculous mother?

The best way to do that is to be sure that the mother is receiving adequate chemotherapy. If she is, then there is very little to no likelihood of transmission of infection, and the child should therefore be protected.

—PHILIP C. HOPEWELL, MD, *San Francisco*

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The Role of Estrogens as a Risk Factor for Stroke in Postmenopausal Women

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The estrogen component in oral contraceptives is generally thought to increase the risk of stroke in users as compared with controls. If this were true, an increased risk for stroke also should be seen among postmenopausal women using estrogens as compared with nonusers. To test this hypothesis, the charts of 198 postmenopausal patients who had had strokes were compared with those of 396 controls for estrogen use and for the associated risk factors of diabetes, hypertension and coronary artery disease. The difference between estrogen use in the study population versus controls proved not significant, and the use of estrogens did not significantly influence the distribution of the above risk factors. We concluded that the use of estrogens in physiological replacement doses does not increase the risk of stroke in postmenopausal women.

THE COLLABORATIVE GROUP for the Study of Strokes in Young Women in 1973 showed that the use of oral contraceptives greatly increases the risk of stroke in users compared with that in normal controls. This initial observation provoked further inquiry into what effects these steroid compounds might have in young women to cause a disease which is usually seen in much older patients. Oral contraceptives contain both estrogens and progestational compounds. Many hypothesized at the time our study was begun that the harmful component was probably estrogen. We reasoned that if this explanation were correct, it could be shown that postmenopausal women taking oral estrogen preparations are at greater risk for the development of stroke than postmenopausal women who do not take estrogens. This study investigates the role of estrogens as an independent risk factor for stroke in postmenopausal women.

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Patients and Methods

The Kaiser Foundation Health Plan provided names and identifying data for all women over the age of 45 years who were discharged from the Northern California Kaiser Foundation Hos-

pitals with a diagnosis of stroke during the years 1972 through 1974. We chose to include only stroke patients discharged from the San Francisco, Redwood City, South San Francisco, Hayward and Santa Clara facilities in the study, as these provided an adequate number of cases representing a broad spectrum of socioeconomic populations. (These facilities serve urban, suburban and rural, industrial and white-collar populations.)

The charts of potential subjects were first reviewed by the neurologist in the team. Only those patients whose records supported the diagnosis of occlusive cerebrovascular disease referable to a specific artery were included in the study. Cases of intracerebral hematoma were excluded, as were such vague diagnoses as "cerebrovascular insufficiency" and "dizziness." The data examined included the history, physical examination and all verifying laboratory x-ray studies, including the results of angiography when available. The distinction between lesions of the internal carotid artery and lesions of its branches—middle and anterior cerebral—was made by either angiographic data or a documented history of transient ischemic attack or attacks in an internal carotid distribution preceding the fixed deficit. The inpatient and outpatient charts for these cases were reviewed by the two physician investigators for the use of estrogens. In addition, the charts were reviewed for evidence of three other recognized risk factors for cerebral and cardiovascular disease, diabetes, hypertension and coronary artery disease. (We attempted to examine smoking histories, but there was so much variation in the amount of information recorded that this was not feasible.)

The criteria for these risk factors were as follows:

- Patients were considered to have diabetes if that diagnosis had been made by their treating physicians or if repeated fasting blood sugar measurements on the chart exceeded our normal laboratory value (110 mg per dl) at the time of the study.
- Patients were considered to have hypertension if repeated blood pressure readings on the chart consistently exceeded 140/90 mm of mercury, or if the attending physician had diagnosed the patient as hypertensive (to include patients who may have had lower blood pressure readings because of antihypertensive medication).

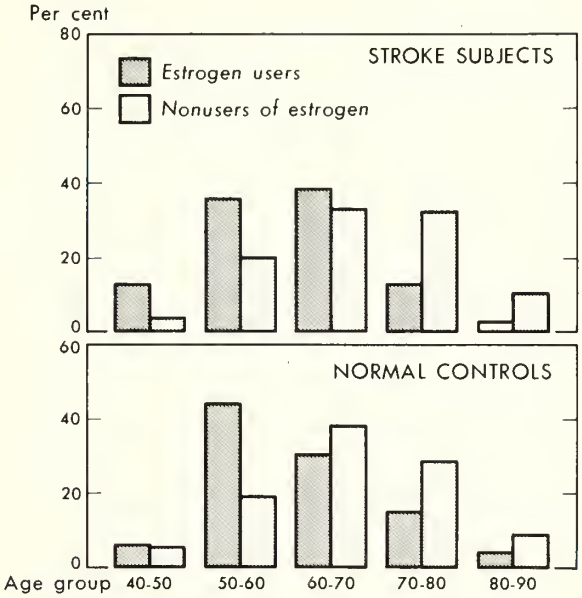

Figure 1.—Age distribution of estrogen users versus nonusers in postmenopausal women who had had strokes and in normal controls.

- Patients were considered to have coronary artery disease if their clinical histories included myocardial infarction, angina pectoris or unexplained cardiac arrhythmias, or if findings on electrocardiograms were interpreted as consistent with coronary artery disease.

In the chart analysis for estrogen use, the specific preparation and duration of use were determined. The subject cases had to be taking estrogens at the time of the stroke, and the control cases had to be using estrogens at the time the subject case to whom they were matched had the stroke.

Some subscribers to the Kaiser Foundation Health Plan obtain some care outside the plan. We therefore wanted to assess if inpatient and outpatient charts used for our study contained complete information on the patients' medical and drug histories. To this end, we mailed questionnaires to our patients covering the information we were seeking in our chart review. Of the 215 questionnaires sent out, 84 were returned, and these showed excellent correlation with the data on the charts.

The subjects were then matched by age and geographic location with normal controls randomly selected from the data bank of the Kaiser Foundation Health Plan. Normal controls were patients who had not had strokes. The criteria for age-

TABLE 1.—*Treatment Histories for Use of Estrogen Medications Other Than Premarin**

Medication	Stroke Patients (8) Dose (mg)	Stroke Patients (8) Duration (years)	Controls (5) Dose (mg)	Controls (5) Duration (years)
Esterified estrogens (Amnestrogen)	0.3	2	None	
	0.625	10		
Ethinyl estradiol and methyltestosterone (Gynetone)	0.2	1	0.2	2
	0.2	2		
Ethinyl estradiol	0.05	5	0.02	10
	0.05	10	0.05	8
Diethylstilbestrol (DES)	0.05	3	None	
	0.05	3		

*Premarin (conjugated estrogens)

TABLE 2.—*Prevalence of Risk Factors Associated With Stroke in 198 Postmenopausal Women Who Had Had Strokes Versus 396 Controls*

Risk Factor	Stroke Patients (percent)	Controls (percent)
Hypertension	55	41
Diabetes	26	5
Coronary artery disease	47	11

matching was that the age of the controls should be within five years of the age of the subject. The criteria for geographic matching was that the control should live in the same city as the subject. For each subject, we obtained two age- and geographic-matched controls. Despite four computer searches, matching controls were not found for 17 patients, who were therefore excluded from the final tabulation. Without exception, the patients who could not be matched with controls were in the 80- to 90-year age group and lived in small communities; none were taking estrogens. A total of 198 subjects and 396 controls remained. The outpatient medical records of the controls were reviewed to confirm that these controls had not had strokes, to assess the same risk factors that were determined for the subjects (diabetes, hypertension and coronary artery disease) and to assess the use of estrogens. The incidence of risk factors was then compared in the subjects and their age- and geographic-matched controls. The data collected from both subjects and controls came from the outpatient charts.

Results

While the age distribution was wide, most of the 198 subjects in our study were between 50 and 80 years of age (Figure 1).

The specific neurological diagnoses recorded for our stroke cases were as follows: (1) occlusion of one of the middle cerebral arteries, 64 percent; (2) occlusion of one of the internal carotid arteries, 22 percent; (3) occlusion in the vertebrobasilar arterial system, 7 percent; (4) lacunar infarction, 5 percent, and (5) occlusion of one of the anterior cerebral arteries, 2 percent.

Of the estrogen preparations used by our subject patients, conjugated estrogens (Premarin) were used by all but eight; and among those using Premarin, all but two were taking either 0.625 mg or 1.25 mg doses. These latter two had been taking 0.3 mg for five years and 2.5 mg for two years, respectively, up to the time of the stroke. The average duration of use of the 0.625 mg dose was 6.85 years and of the 1.25 mg dose was 5.9 years preceding the stroke.

Among the controls who used Premarin, all but five patients were taking 0.625 mg or 1.25 mg per day. Of these five, four patients had taken 0.3 mg of Premarin daily for an average duration of three years preceding the time of stroke in the matched subject patients, and one patient had been taking 3.0 mg daily for a year. In the remaining controls, a third had been taking a 0.625 mg dose of Premarin for an average duration of 7.6 years, and two thirds had been taking 1.25 mg for an average of 7.15 years preceding the time of stroke in the matched subject patients. These doses of conjugated estrogens represent physiological doses for menopausal replacement therapy. The treatment histories of stroke patients and controls taking medications other than Premarin are listed in Table 1.

Of the patients who had had strokes, 20.7 percent had been taking estrogens; in the control group, 18.4 percent were taking estrogens. This difference was not significant ($x^2 = 0.4396$). The relative risk of stroke was estimated (by the relative odds method) to be 1.16 times as great in estrogen users as nonusers, with 95 percent confidence limits[2] of 0.75 and 1.77.

As expected, those risk factors which have been associated repeatedly with stroke were more prevalent in our stroke population than in the controls (Table 2).

We endeavored to see if the use of estrogens influenced the distribution of the risk factors by reanalyzing our data with cases and controls pooled. Hypertension was found in 45.6 percent of the estrogen users and 46 percent of the non-

users. Coronary artery disease was found in 22.8 percent of the estrogen users and in 22 percent of the nonusers. Diabetes was found in 6.1 percent of the estrogen users and 14 percent of the nonusers. Because of this last observation, the relative risk of stroke in the estrogen users and nonusers was recalculated after the factor of diabetes had been removed. After removal of patients with diabetes from the population, the percentage of stroke patients using estrogens was 24.0 percent and the percentage of control patients using estrogens was 19.3 percent. This difference was not significant ($x^2 = 1.43$). (The relative risk of stroke in estrogen users compared with nonusers was estimated to be 1.32, with 95 percent confidence limits of 0.84 and 2.09.)

Our data show that the risk factor of use of estrogens in our patients who had had strokes was no different from that among users of estrogens in the population of matched controls. In addition, the risk factors of hypertension, coronary artery disease and diabetes coupled with estrogen use did not increase the risk of stroke above that associated with these factors alone.

Discussion

This study was preceded by a large body of medical literature linking oral contraceptives with cardiovascular disease. In addition to their 1973 study,[1] which provided the stimulus for this research, the Collaborative Group for the Study of Stroke in Young Women also reported in 1975[3] that oral contraceptives are an independent risk factor and do not act by augmenting the effect of other risks such as hypertension, smoking or migraine.

Mann and associates[4] reported in 1975 that oral contraceptive use was considerably more frequent in women who had nonfatal myocardial infarctions. This risk factor appeared to prevail even in the absence of cigarette smoking, hypertension, diabetes, hypercholesterolemia, toxemia of pregnancy or obesity. The risk of death from myocardial infarction in their studies was estimated to be 2.8 times greater in current users of oral contraceptives who were 30 to 39 years of age and 4.7 times greater in current users who were 40 to 44 years of age.

The Stanford Three-Community Study in 1976[5] described a differential effect of oral contraceptives versus pure estrogens on cardiovascular risk factors. The study found a more profound elevation of plasma triglyceride and a greater degree of hypertension in users of combination oral contraceptives than in users of pure estrogens, and that this difference correlated with the amount of progesterone and not the amount of estrogen in the preparation.

The physiological doses of estrogens used for menopausal replacement therapy are from a half to a sixth as potent as the estrogens contained in the oral contraceptives.

These physiological doses are, however, the same dosages which have been implicated as carcinogenic for endometrial carcinoma and as a form of protection in postmenopausal women against osteoporosis.

The purpose of this study was to find if there was an increased risk of stroke in women after menopause who were taking physiological doses of estrogens for the postmenopausal syndrome compared with women who did not use these hormones.

After we had completed our independent study but before its publication, Pfeffer and van den Noort[6] reported the results of a study similar to ours conducted among postmenopausal women aged 58 through 95 years in a California retirement community. The findings of that study agree with ours in that the use of estrogens in physiological replacement dosages did not increase the risk of stroke in postmenopausal women.

The Boston Collaborative Drug Surveillance Program[7] reported in 1976 that the regular use of estrogens after menopause did not increase the risk of nonfatal myocardial infarction. Of 336 patients who had sustained myocardial infarctions, 2.4 percent were regular users of estrogens; 4.9 percent of the controls were regular users of estrogens as well. The Boston study data do not support the suggestion that estrogen use has a protective effect against nonfatal myocardial infarctions, but rather that estrogen use has no effect.

The incidence of estrogen replacement among our patients was four times greater than that of the Boston study. Similarly, the study of Pfeffer and van den Noort[6] detected a much higher percentage of women receiving estrogen replacement therapy than that found in the Boston study. We cannot readily explain this difference except to note that the differences in style of practice, patient demand and, possibly, socioeconomic levels

may explain the higher percentage of estrogen use in our population.

Many factors must be evaluated when deciding if a particular patient should receive estrogen replacement during menopause. The potential risk of endometrial carcinoma is an important factor, as well as the potential adverse effect of estrogens on coexistent hypertension. Nonetheless, some postmenopausal women require estrogen replacement therapy to allow them to function adequately.

The benefit/risk factor of estrogen replacement therapy must always be scrutinized. The results of this study show that use of estrogens in physiological replacement doses is not associated with increased risk of stroke in postmenopausal women.

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Hip Fracture, Skeletal Fragility, Osteoporosis and Hormonal Deprivation in Elderly Women

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Fractures of the hip have been shown to have a significant personal and societal impact in Western countries; this impact is largely borne by elderly women, and represents a substantial health care commitment in modern society. For many people a fracture of the proximal end of the femur represents a preterminal event of considerable cost, both in economic loss and psychosocial well-being. These fractures are generally recognized as a clinical complication of osteoporosis, and are one index of general skeletal fragility which is also manifested in fractures of the vertebrae and of the distal radius (Colles fracture).

There is increasing evidence that hormonal deprivation in elderly women is directly related to loss of skeletal integrity and consequent fragility. There is also increasing evidence that hormonal substitution is effective in preventing this structural loss and fragility. Unfortunately, a therapeutic dilemma has arisen in that the preparation that seems to give optimal protection, conjugated estrogens, has also been reported to cause an increased incidence of endometrial carcinoma. The search for a preparation or dosage regimen of estrogens which simultaneously prevents skeletal atrophy and fragility and avoids the increased risk of malignancy must be a long-term goal.

FRACTURES OF THE HIP have been shown to have serious personal and social impact and represent a substantial commitment of medical care resources among Western societies. Fractures of the hip in the elderly are associated with all the commonly recognized indices of impaired health (such as disability, discomfort, social disruption and dissatisfaction), frequently lead to fatal complications, and are an index of general skeletal fragility. The impact and effect of these fractures is borne largely by elderly women. Many studies have shown that hip fractures occur more frequently at all ages in women, and increase to as much as nine times as often in women over age 60.[1]

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Impact of Hip Fractures

Wylie,[2] in surveying Medicare data for 1967, found that the rate of femur fracture as measured by discharge diagnoses from acute care hospitals in the United States was 909 per 100,000 white

women 65 years of age and older and enrolled in Medicare, representing an incidence rate of almost 1.0 percent per year. The rate doubled in men and women 80 to 84 years of age, with a ratio of approximately three women to one man overall.

Bauer[1] estimated that in Malmö, Sweden, in 1955 the annual fracture rate for the femoral neck was 220 per 100,000 women between the ages of 65 and 69. This increased to 1,170 per 100,000 women 80 years or older, an incidence rate of almost 1.2 percent per year.

Morgan[3] estimates the frequency of femoral neck fractures in Europe as rising from less than one per 1,000 (per ten-year span) in early life to over 12 per 1,000 by age 90. He further estimates the cumulative probability of fracture of the neck of the femur as approaching 30 percent by age 90, assuming that all persons at risk survive to that age, a disconcerting demographic surmise as longevity increases. Alffram[4] also gives the cumulative risk in Sweden of sustaining at least one cervical or intertrochanteric femoral fracture before age 90 as nearly 25 percent. It must be noted that genetic variations are considerable and northern European gene pools apparently involve substantially increased risk.[5]

Alffram[4] studied 1,664 fractures of the proximal end of the femur in Malmö between 1949 and 1961. The mean age was 73 years in women and 69 years in men, with 86.0 percent of the patients being older than 60. These fractures were 2.4 times more frequent in women, and women who had previously sustained a fracture of the distal radius (Colles fracture), another index of skeletal fragility, were at even greater risk as age advanced. The observed number of fractures of the femur nearly doubled the number expected among women between ages 75 and 79, if preceded by a distal forearm fracture.

Beals[6] studied the incidence of hip fractures in Portland, Oregon, in a population which fairly represents a demographic cross section of at least one half of the major urban areas in the United States. He found that there was a peak incidence at 78 years of age, that 8.5 percent of the cases had already sustained one previous hip fracture, and 4.6 percent had other associated fractures. At the end of one year following the fracture, only 50 percent of these patients remained alive. After four years, only 15.0 percent of the men and 41.0 percent of the women 75 years or older were still alive. These findings confirmed the results of an earlier study in Norway by Mikkelsen and Langholm,[7] which showed greatly increased mortality during the first four years after proximal femoral fractures.

Sweet and co-workers[8] studied associated morbidity and mortality in 53 cases of fractures of the proximal femur. The mortality was 21.7 percent in the transcervical and 16.6 percent in the intertrochanteric group while in hospital. Morbidity was given as 56.5 percent and 60.0 percent, respectively. Newton-John and Morgan[9] came to the following conclusions:

> (1) all persons lose bone with age; (2) there is so far no evidence that osteoporosis in the older population is the result of either an excessive rate of loss or an abnormal total loss of bone; and (3) the risk of fracture is largely determined by the amount of bone, and the increase in frequency of fracture with age is largely determined by the normal loss of bone with age.
>
> The increase in the frequency of fractures of the femoral neck is approximately exponential, whereas the loss of bone with age in [sic] linear. Fractures happen in persons with the thinner bones and it follows from the characteristics of bone loss with age, that the frequency of "thin bones" however defined, increases exponentially with age.

Kohn and co-workers,[10] in a study of all patients 80 years and older at the University Surgical Clinic in Vienna, found that 338 of 599 patients, or 56.4 percent who required operations for any reason, required them for hip fractures. An additional 41 or 6.8 percent required operations for other fractures. There were 72 deaths in the hip fracture group. A total of 403 or 83.0 percent of the patients requiring surgical procedures for trauma were women.

Barnes and colleagues,[11] in a large retrospective study of subcapital femoral fractures in Great Britain, found that 395 of the 1,618 patients (24.4 percent) died before the results of the treatment could be evaluated; 7.4 percent of the women and 13.3 percent of the men died within a month of operation. Approximately a third of displaced fractures failed to unite (presumably with increased likelihood of additional operations). The likelihood of nonunion increased with age. Late segmental collapse, presumably on a vascular basis, developed in 24.0 percent of the women and 15.0 percent of the men, and was physically disabling in 29.0 percent of this subset.

Data from the Medicare program[12] can be used to provide evidence of the economic impact of fractures of the neck of the femur among elderly women. In 1973 fracture of the neck of the femur

was the fifth most frequent diagnosis at hospital discharge among women in the program. The mean length of hospital stay for these fractures among women was 22.3 days as compared with a mean length of stay of 11.2 days for all other discharges among both sexes. The mean charge per hospital stay for fractures of the neck of the femur was $2,263 compared with $1,176 for all other diagnoses (given in 1973 dollar amounts). Hospital charges for such fractures among women 65 years and older in the Medicare program in 1973 were estimated to be $212 million. This will undoubtedly increase as more women continue to live longer.

Hip Fractures and Osteoporosis

Hip fractures in the elderly are generally recognized as a clinical complication of osteoporosis. In the early 1820's, Sir Astley Cooper in his *Treatise on Dislocations and on Fractures of the Joints*[13] made the following observations:

> the fracture of the neck of the thigh bone within the capsular ligament seldom happens but at an advanced period of life. . . . That regular decay of nature which is called old age is attended with changes which are easily detected in the dead body; and one of the principal of these is found in the bones, for they become thin in their shell and spongy in their texture. . . . Women are much more liable to this species of fracture than men.

These early and astute observations of the relationships between age, sex, loss of bone substance and fracture of the proximal femur have been amplified and verified by 1½ centuries of subsequent medical research, but to this day there is no consensus on prophylaxis. Our understanding of osteoporosis traces its modern concepts to Fuller Albright, who in 1941 wrote that osteoporosis is a "condition in which there is a lack of bone tissue but that which remains is fully calcified."[14] He believed it was caused by deficient formation of bone.

Osteoporosis is generally recognized as a disease predominantly of the axial skeleton, appearing as a reduction of mass of both cortical and cancellous bone in the vertebrae, ribs, pelvis and the neck of the femur. Both epidemiologic and clinical studies have shown the association between fractures of the neck of the femur, the distal radius and the vertebrae and osteoporosis.

Lender and co-workers[15] examined the prevalence of osteoporosis in Jerusalem between 1967 and 1971 in a general population and among patients with fractures of the neck of the femur. Using identical criteria applied to lateral x-ray films of the lumbar spine they reported a prevalence rate of osteoporosis of 14.5 percent among women in the general population and of 37.8 percent among women with femoral neck fractures.

Iskrant and Smith[16] studied the coincidence of osteoporosis (diagnosed by relative vertebral density determined by lateral roentgenograms of the dorsolumbar spine) and fractures in women aged 45 years and older for a three-year period. The annual fracture rate was 3.6 percent, and varied from 2.0 percent among those without osteoporosis to 7.0 percent in those with the condition. The closest associations were with fractures of the upper femur, radius, ankle and wrists.

Nilsson,[17] in a study of women 50 years and older, showed a significantly lower "head plus trunk height" to "total height" ratio in patients with proximal femoral fractures than in age-matched control patients with a variety of other orthopedic conditions. He also detected significant weight disparity. This association is thought to be a result of shortening of the spine because of vertebral fracture caused by osteoporosis. This has also been shown by Gordan.[18,19]

Urist and colleagues[20] studied 100 postmenopausal white women with radiologic osteoporosis (shown by multiple vertebral fractures) for periods ranging from 7 to 20 years. These women, most of of whom were between 60 and 70 years of age at the time of first observation, were engaged in the usual activities of daily life for their age and sex. Nine sustained at least one long-bone fracture during the observation period and two sustained femoral neck fractures, for an overall fracture incidence of 11 percent.

Alhava and Karjalainen[21] showed that the mean bone mineral content of the trabecular radius was significantly lower than normal in both sexes when the index event was a fracture of the hip. Nordin and co-workers[22] believe that postmenopausal osteoporosis is a self-limiting process in cancellous bone but a continuing process in cortical bone, at least as measured in the metacarpals. They believe the age-related increase in frequency of distal forearm fractures reflects the situation in cancellous bone, and the increase in femoral neck fractures reflects the situation in cortical bone, thus explaining the progressively increased frequency of the latter as age advances.

Reeves[23] studied the uninjured, excised, proximal femur of 37 patients who had died within a

year of metallic prosthetic replacement for fracture of the contralateral hip. All had walked after the replacement. Loading to failure of these femurs was positively correlated with bone mass studies (on both femoral heads) as well as with roentgenographic and postmortem estimations of the thickness of the cortical bone. The results suggested that there is a group of elderly women in whom fracture of the femoral neck may occur under the load (about three times body weight) imposed by quiet walking with a reduced bone mass. Singh and co-workers[24] described changes in the roentgenographic patterns and numbers of trabeculae in the femoral head and neck, which they were able to correlate statistically with histological grading of iliac crest biopsies, the occurrence of femoral head and neck fractures, and the degree of trauma which had caused the fracture. These studies seem to substantiate the notion that loss of bone in the proximal femur occurs as a part of a generalized process (osteoporosis), and predisposes to bone failure under ordinary stresses of walking or stumbling.

Vose and colleagues[25] showed an increased ash content and increased strength per unit volume of cortical bone of osteoporotic femurs, compared with nondiseased femurs, in spite of which the overall strength of the osteoporotic femurs under static loading was reduced by approximately 40 percent. They concluded that the weakness which leads to fractures is a quantitative, and not a qualitative phenomenon, that is, due to "atrophy of the cortical wall." Alhava,[26] in a study of 81 women and 23 men who had sustained hip fractures from moderate or insignificant trauma, concluded that senile osteoporosis was the most important predisposing factor. The mean age of this group of patients was about 72 years.

Loss of Ovarian Function and Bone Mineral Content

Dalen and colleagues[27] assayed the bone mineral content in women who had had oophorectomies and in those who had not had this operation by means of x-ray spectrophotometry in five different parts of the skeleton. They were able to show an average diminution of 18 percent in mineral content of mainly trabecular parts of the skeleton (distal radius and ulna, third lumbar vertebra, femoral neck), in contrast to cortical parts, and concluded that increased fracture risk existed in these areas. Meema and Meema[28] have shown by densitometric and morphometric roentgenographic bone measurements that there is an age-related decline in bone mineral content in women that is progressive. They noted in their study that women of all ages, but especially after age 60, with both vertebral compression fractures and femoral neck fractures fell below the mean for mineral mass and cortical thickness of the radius for their age group. Virtually all fell more than two standard deviations below the mean for younger (less than 50 years) women, whose bone strength can, generally speaking, be assumed to be adequate to the stresses imposed on it.

Dequeker[29] has shown that cortical area, measured by metacarpal width, declines progessively with age in women, and that women with hip fractures fall consistently below the age-adjusted mean regression line for cortical metacarpal width. Interestingly, fractures of the surgical neck of the humerus did not correlate well, while those of the lower end of the radius did. He also was able to correlate, positively, in cadaver specimens, trabecular bone mass of iliac crest specimens and cortical bone mass measured on x-ray films of the right second metacarpal, again suggesting generalized skeletal hypoplasia.

Foss and Byers[30] have also shown that patients with fractures of the upper end of the femur have a less than normal metacarpal index and almost never have osteoarthrosis, which instead correlated with an increased metacarpal index. This confirmed an earlier study[31] done with trephine biopsy photomicrograph specimens of iliac crest bone, which suggested that there was a substantially higher incidence of osteoporosis in patients with femoral neck fractures.

Khairi and co-workers[32] studied the fracture-predicting usefulness of the femoral trabecular index (Singh) and bone mineral measurement by photon absorptiometry in 106 white women 70 to 95 years old. A positive correlation was found between the Singh index and the bone mineral content, but it was not useful in predicting subsequent fractures.

While most data available show that bone loss is related to advancing age, there is also substantial evidence suggesting that bone loss in women is related to loss of ovarian function rather than to aging as such. The extent of bone loss appears to be a function of the number of years after menopause, either natural or surgical. Such findings have been reported by Meema and Meema[28] by comparing bone mineral mass of the radius measured by radiographic photodensitom-

etry in postmenopausal and premenopausal women. Similar conclusions have been reached by Nordin and colleagues,[33] who measured cortical thickness of the second metacarpal; by Aitken and co-workers,[34,35] who assessed radiographic density of the third metacarpal; by Heer and colleague[36] who examined bone mineral mass of the radius with photon absorptiometry; by Dalen and co-workers[27]; by Heaney[37]; and in a sequential study by Nordin and colleagues.[38]

Thus, it appears compelling to this observer that fractures among elderly women, notably compression fractures of the vertebrae, distal radius and proximal end of the femur are the result of loss of bone mass. That bone loss occurs in the proximal femur as age advances has been shown, and that such bones are more prone to fail under stress is also clear. It also appears that loss of bone mass in women is directly related to loss of ovarian function, whether occurring naturally or induced by surgical means; further, the longer the postmenopausal period the greater the loss in bone mass.

Osteoporosis and Estrogen Administration

The apparent relationship between loss of ovarian function and the cause of postmenopausal osteoporosis has led to estrogen therapy being the choice of many workers for both treatment and prevention of postmenopausal osteoporosis. Data to support such use of estrogens have been adduced by Henneman and Wallach,[39] Davis and co-workers,[40] and Meema and Meema.[41] These early studies indicated that estrogen therapy given after oophorectomy may at best only delay the onset of bone mineral loss with age. More recent evidence by Aitken and co-workers[34,42] has shown that relatively small dosages of estrogen will prevent, and if given early enough, will reverse such losses of bone mineral content. In a controlled double-blind study, estrogen therapy (mestranol), started within two months of oophorectomy, effectively prevented bone loss, and started three years, but not later than six years, after oophorectomy caused a highly significant increase in bone mineral content compared with untreated controls.

Meema and co-workers[43] were also able to show a significant preventive effect of estrogen therapy on postmenopausal bone loss both in castrates and following natural menopause in 82 women evaluated twice at four- to ten-year intervals. Those most frequently used were equine conjugated estrogens in doses of 0.625 or 1.25 mg per day. Recker and Heaney[44] studied the cases of 60 postmenopausal women who had been divided into three groups: (1) those receiving no estrogen; (2) those receiving 0.625 of conjugated estrogens and 5 mg of methyltestosterone 21 days of each month, and (3) those receiving 2.6 grams of calcium carbonate per day. In women in the hormone group and the calcium group there was significant diminution in the rate of bone loss when measured by radiography, but protection was noted in those in the hormone group only when measured by photon absorptiometry. Horsman and colleagues[45] confirmed that estrogen administration prevents bone loss in a prospective study of the cases of 72 postmenopausal women followed for two years.

Lindsay and co-workers[46,47] showed that in women who had had oophorectomies continuous estrogen therapy had been effective in preventing bone loss for eight years, the length of their observations. On the other hand, the women who had discontinued estrogen therapy after four years showed the same amount of bone loss as those who had had oophorectomies and who were not receiving estrogen therapy.

Thus, there is substantial evidence accumulating to indicate that estrogen therapy is effective in preventing postmenopausal osteoporosis as measured by a reduction in bone mineral content. It also appears that both the timing and the length of estrogen therapy influence the rate and the amount of bone loss. That estrogen therapy can prevent the clinical complications of osteoporosis, such as fractures of the neck of the femur is also becoming clearer. Hutchinson and co-workers[48] were able to show a protective effect of postmenopausal estrogens, on both hip and distal radius fractures, with an odds ratio of 3.8 if started within five years of menopause.

The Prophylactic Dilemma

Recent reports[49-52] of an increased incidence of endometrial carcinoma, ranging from 4.5 to 12.5 times the expected rate, among long-term estrogen users has resulted in widespread professional concern and likely has diminished the frequency of its use. The effects of estrogens on the endometrium are difficult to interpret, however, and misdiagnosis of adenomatous hyperplasia as endometrial carcinoma, combined with increased scrutiny of estrogen users,[53] may have resulted in an overestimation of the frequency of this problem. Another study[54] of long-term estro-

gen use after hysterectomy has indicated that overall mortality from all causes, including cardiovascular and neoplastic, was lower than expected. Under any circumstances accurate epidemiologic data will be necessary to evaluate the relative risk of death and disability from hip fracture and from malignant conditions. The choice is not clear at this time and remains difficult to make once both sides of the controversy are fully developed.

Additional preparations and lower dosage regimens of conjugated estrogens have also been suggested in the approach to this problem. Geola and associates[55] have recently shown that as little as 0.3 mg of conjugated equine estrogens given orally can cause reversion of the calcium/creatinine ratio to premenopausal levels as early as six weeks after initiation of therapy. The relationship of the calcium/creatinine ratio to bone metabolism, however, is only inferential with regard to the prevention of fracture. It, nonetheless, indicates that a dosage regimen, smaller than that associated with malignant conditions of the uterus, may be effective. In a study by Recker and colleagues[44] conjugated equine estrogens and methyltestosterone were used in one regimen and calcium carbonate in another in menopausal women. When radiographic estimation of metacarpal cortical thickness was carried out, the hormone and the calcium regimens both appeared to show significant reduction in the rate of decrease of skeletal mass. However, when studied by photon absorptiometry only the hormone group showed a significant protective effect compared with controls.

Horsman and co-workers,[45] in a prospective trial of 72 postmenopausal women whose cases were followed at least two years, showed that the group treated with estrogens lost no bone by either densitometry or determination of metacarpal thickness. The calcium-treated group showed intermediate bone loss between that of the control group and that of the estrogen-treated group, thus, indicating less than optimal results from this technique.

Calcitonin has also been suggested as a method of management of osteoporosis; Wallach and colleagues[56] showed in a small series that approximately 50 percent of patients will respond to the use of calcitonin. They found that total body calcium, as measured by in vivo neutron activation analysis, increased in 12 patients; however, an additional 13 treated in the same manner did not change or showed a decrease of total body calcium. In addition, it was noted that antibodies developed in six patients. Chestnut and co-workers[57] studied the cases of women given calcitonin in combination with calcium carbonate and vitamin D_2 for 18 months. They were able to show an increase in total body calcium as measured by neutron activation analysis; however, antibodies were detected in 18 of 26 patients in the treatment group. It seems to this observer that medical history clearly indicates that one must be circumspect about chronic medical treatment with any preparation which is likely to produce immune responses in the patient. Further work is clearly indicated in this area before it can be recommended for use in other than a controlled research setting.

Lindsay and co-workers[58] have shown in a preliminary randomized trial carried out over a year that intramuscularly given progestogen (Gestronol) as well as mestranol can prevent bone mineral loss as measured by photon absorptiometry. More work will be required in this area as well.

The use of fluoride and calcium has also been suggested in the management of osteoporosis. In a recent paper, Riggs and co-workers,[59] reported on the cases of 36 patients with primary osteoporosis who were treated up to six years with sodium fluoride, calcium supplements and, in 24 patients, vitamin D. Major adverse reactions, including synovitis, painful plantar fascial syndrome, recurrent vomiting or anemia occurred in 15 of this group, representing a 42 percent complication rate. New vertebral fractures continued to occur at an alarming rate for at least the first year of therapy, indicating a considerable lag phase if this treatment is effective at all. This group concluded that "until long-term safety and antifracture efficacy are better established, this regimen should continue to be restricted to investigational use."[59]

Conclusion

It appears that the search for a preparation or dosage regimen which simultaneously prevents skeletal atrophy and fragility, and avoids the increased risk of malignancy must be a long-term goal. What is not acceptable is unquestioning subservience to the idea that a possibly increased risk of uterine malignancy must sweep aside all considerations of morbidity and mortality from hip fractures that might be prevented.

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Nutritional Aspects of Magnesium Metabolism

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The absolute necessity for magnesium in plant and animal nutrition is easily appreciated when one realizes that magnesium is found in high concentration in cells. It is necessary for photosynthesis in plants and for all reactions involving adenosine triphosphate in plant and animal cells. Although it is abundant in nature in general, deficiencies occur in both plants and animals. Human beings need about 5 mg of magnesium per kg of body weight per day. Infants and young children need twice as much. Children and women during pregnancy or lactation require significantly greater amounts than normal adults. Various diseases result in a deficiency of magnesium because of interruption of food intake or intestinal or renal wasting of the mineral.

IT WAS DISCOVERED that plants have an absolute need for magnesium (Mg) for growth when it was found in 1860 that plants raised on an entirely synthetic medium would not grow without this mineral. Magnesium protoporphyrin is an obligate part of the chlorophyll molecule, so that the entire chain of food and of fossil fuels has depended on its presence. Furthermore, magnesium has a vital role in all phosphate-dependent metabolic processes of plants and animals. Naturally occurring magnesium deficiencies in plants have been clearly documented in regions in which there is a low content of the mineral in the soil. For example, sand brown of tobacco was recognized in 1922. Subsequently, such deficiencies have been found in potatoes, apple trees and other plants. Magnesium deficiency is manifested by fading of the green color of leaves and by early defoliation. The Atlantic coastal plain between Maryland and Florida has many areas in which the soil has a marginal content of magnesium. The beneficial effects of using magnesium-enriched fertilizers were first shown in the 19th century; now such fertilizers are used to replenish soil found by chemical analysis to be depleted. Cattle raised on grass grown in soil that has a low Mg content are susceptible to the development of a magnesium deficiency. However, as mentioned above, this condition can be prevented by appropriate fertilization of the soil.

It was suspected that magnesium played an important role in animal nutrition even before it was proved conclusively by Leroy in 1926.[1] He was the first to show that mice stopped growing and later died when placed on a Mg-deficient diet. The need for magnesium in the growth of weanling rats is dramatically illustrated in Figure 1 (Griffith JA, Flink EB: Unpublished data, 1962). In 1932 Kruse, Orent and McCollum[2]

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ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
Mg = magnesium
TPN = total parenteral nutrition

conducted experiments—which are now considered classic—on magnesium deficiency in rats, by using a diet with 1.8 parts of Mg per million. Many other studies have followed. In some ways rats respond uniquely, particularly with regards to metabolism of calcium (Ca). Magnesium deficiency in rats results in significant aminoaciduria.[3] This accounts in part for their failure to thrive and grow. Young animals are more vulnerable to the effects of diets deficient in magnesium than are mature animals.

Spontaneous hypomagnesemia occurs in cattle, other ruminants and horses. In 1929 Sjollema[4] found hypomagnesemia in cattle, which usually occurs during the first few weeks of grazing in the spring, or after calving. The cows become restless, nervous and unsteady, have muscle twitching, grinding of teeth, rolling of the eyes and, finally, convulsions. It was called kopziekte by Sjollema which, unfortunately, was translated as grass tetany or grass staggers. A better literal translation would have been grass epilepsy, because tetany is not an accurate descriptor. This syndrome also develops in calves fed only milk for prolonged periods. In this instance the very high calcium content of milk competes with the much smaller amounts of magnesium for absorption. Young animals need much more Mg than mature animals. So too, infants, young children and pregnant or lactating women have much greater need for this mineral than other humans.

Biochemical Aspects

Some biochemical facts should help us understand certain vital aspects of magnesium metabolism. In photosynthesis magnesium is ionically bound in the center of the protoporphyrin molecule and apparently stabilizes the structure, so that it undergoes a perfectly reversible one-electron oxidation. The oxidation-reduction potential of chlorophyll correlates very well with the electronegativity of the central Mg ion. The chlorophyll molecule harvests light like a light meter.[5] The energy for synthesis of carbohydrate from carbon dioxide and water is derived from light

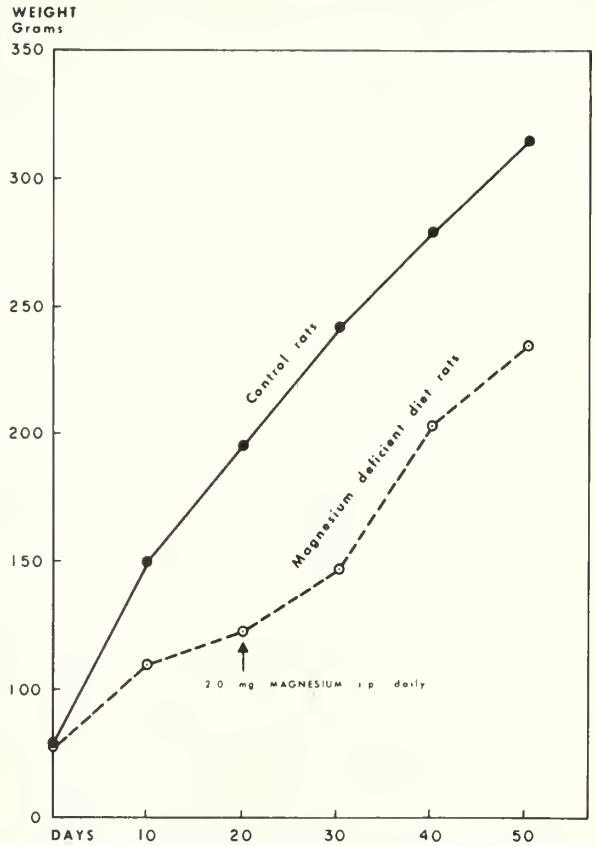

Figure 1.—Six weanling Sprague Dawley rats were given Purina Dog Chow, and six weanling rats were given a diet severely restricted in magnesium, which resulted in slow growth. Rats maintained on this severely deficient diet begin to lose weight after 20 days and all die within 30 to 40 days if left untreated. However, at 20 days, the six diet-restricted rats were injected intraperitoneally with 2.0 mg of magnesium (magnesium sulfate, $MgSO_4$). Treatment continued daily with obvious resumption of normal growth.

via chlorophyll and 12 separate enzymes catalyzed by adenosine triphosphate (ATP). Magnesium is a cofactor for ATP in all transphosphorylation reactions. It is a cofactor for many enzymes. In the absence of sunlight, plants use stored energy by way of oxidative phosphorylation. Animal cells, of course, derive their energy from oxidative phosphorylation which produces ATP. Phosphorylation in chloroplasts is light-dependent, but phosphorylation in mitochondria is dependent on oxygen and not on light.

The generation and use of ATP is dependent on magnesium—therefore, the synthesis of all proteins, including enzymes and hormones, nucleic acids, nucleoproteins, nucleotides, lipids and carbohydrates, as well as activation of formate, acetate and sulfate, transfer of methyl groups and muscle contraction. Magnesium acts to stabilize

ribosomes so that they do not dissociate into smaller particles and interrupt polypeptide synthesis. The size of RNA aggregates depends on optimum concentration of magnesium; therefore, polypeptide formation depends on magnesium as well.[5] The high concentration of magnesium and phosphate in cells is of obvious physiological importance.

Nutritional Requirements

Determining nutritional requirements for magnesium depends on analytical methods. At present the most precise method available is the one using atomic absorption spectrophotometry. The Perkin Elmer manual[6] describes details of such atomic absorption analyses. Important aspects of earlier techniques are discussed in detail by Alcock.[7] A great deal of knowledge has been gained by use of these somewhat less precise earlier quantitative methods.

A normal human conserves magnesium avidly as shown by several studies. Fitzgerald and Fourman[8] restricted the magnesium intake of two healthy men to 1.1 mEq per day for 22 days in one and 27 days in the other. The restricted diet resulted in a loss of 42 and 72 mEq of magnesium, respectively. No symptoms developed in either man and serum levels of Mg did not fall significantly. Shils[9] conducted a much more rigorous and prolonged study of dietary restriction in which only 0.7 mEq of magnesium per day was given for 42 to 117 days in six subjects and 266 days in one subject until pronounced symptoms developed. Levels of magnesium in the urine decreased to 1.0 mEq or less per day in all subjects within seven days. However, this drop occurred before there was significant decrease in serum levels of Mg. His elegant experiments illustrate the extraordinary ability of the kidneys to conserve magnesium. He also produced symptomatic magnesium deficiency that was fairly severe in some subjects by permitting no intake of the mineral for long periods. In his experiments all other nutrients were kept within adequate range so that no other form of malnutrition occurred.

Early techniques were cumbersome; however, over the years steady progress has been made in assessing nutritional requirements for magnesium in healthy subjects. Balance techniques, in use since 1915, are tedious and short testing periods can be somewhat misleading unless there is good agreement among the findings of all subjects involved in a given study. It is not surprising that there still are differing opinions about daily requirements. Certain factors adversely affect the magnesium balance in normal humans and in experimental animals. These include high levels of calcium, protein and phosphate.[10-12] A liquid protein diet recently popularized for weight reduction has been associated with serious metabolic consequences. This high nitrogen diet relative to other nutrients causes the depletion of magnesium.[13] Excessive alcohol intake is a very important factor in causing Mg deficiency as well. When any of these factors are present, more Mg is needed in the diet to maintain a necessary balance.

A study of a group of 16 normal adults and 11 obese adults on a metabolic ward was done.[14] An intake of magnesium of less than 3 mg per kg of body weight per day in the normal subjects and of 1.8 mg of magnesium per kg of body weight per day in obese subjects resulted in a slightly negative balance. However, an intake of 3.6 to 4.2 mg per kg of body weight per day in the normal adults and greater than 1.8 mg per kg of body weight per day in the obese adults resulted in a zero or positive balance. The total intake ranged from between 204 and 336 mg of magnesium per day. To attain higher intakes of Mg than this, persons eating typical American diets would have to consume more calories[15] or take Mg supplements.

In the subjects cited above who were receiving less than 144 mg of magnesium per day, 78 mg (58 percent of the intake) appeared in the urine per day. However, in those receiving more than 159 mg per day (range 159 to 288 mg), 45 percent of the intake was recovered in the urine, with a mean of 104 mg. Heaton[16] has shown a similar phenomenon. The absolute amount of magnesium absorbed and excreted by the kidney, therefore, is greater when the intake is high, so that the absolute amount absorbed correlates directly with the intake. In a study of young college women, a slight positive or zero balance of magnesium was maintained on an intake of approximately 260 mg of the mineral per day.[12] The addition of calcium or phosphate (or both) decreased the balance somewhat. In a summary of her review of the literature on balance studies in normal subjects, Seelig[17] concluded that the daily requirement of magnesium is not 300 mg per day or even 5 mg per kg of body weight per day, but probably at least 6 mg per kg of body weight per day. Others agree that this latter amount is needed by

adults.[18,19] It is clear that a definition of the ongoing need for magnesium is subject to variable interpretation. Except in rare cases of persons with renal wasting of magnesium, a zero or positive balance can be maintained by an intake of 4.0 mg per kg of body weight per day. Additional intake of magnesium may have beneficial effects, and this possibility is being investigated. The recommended daily allowances will be discussed below.

On an average, the amount of Mg excreted in the urine is 35 percent to 45 percent of the daily intake. The excretion into the urine of the radioactive isotope ^{28}Mg, which was administered to normal men without gastrointestinal tract abnormalities, was 41 percent ± 8 percent.[20] This value corresponds very well with balance studies of normal subjects noted above. When ^{28}Mg was injected intravenously into a normal human subject, only 1.8 percent of the injected radioactive agent was recovered in the stool within 72 hours.[21] This agrees with nonisotopic studies too, namely that any excess magnesium after parenteral administration is not excreted in the feces but in the urine.

The magnesium content of food as calculated from tables of food composition and from chemical analysis shows that in a mixed general American diet it is very closely correlated with the total number of calories consumed.[15] This calculation breaks down, however, when an inordinate amount of calories is derived from refined sugars or alcohol, both of which contain neither magnesium nor other minerals. An important consideration regarding food intake is that refined sugar and processed food such as refined flour from wheat and polished rice from unpolished rice all lose a great deal of magnesium and calcium in processing.[19] This is a good reason for eating less refined foods, particularly whole cereal grains.

The Mg content of water may be of significance in nutrition. Magnesium and calcium are usually found together in hard water. Many studies of hard water versus soft water in different regions of the world have focussed on the relationship between hard water and, especially, its magnesium content and mortality from coronary artery disease. Such studies have been carried out in Australia, Belgium, Canada, Czechoslovakia, Finland, Holland, Ireland, Italy, Japan, Sweden, the United Kingdom, the United States, the USSR and West Germany.[19] There are widely differing points of view. In a recent study carried out in Hull and Burnley, England, the investigators found a greater mortality from coronary artery disease among persons living in the hard water region of Hull compared with those living in the soft water area of Burnley.[22] This finding is contrary to most studies, and a clear relationship between a "water factor" and cardiovascular health has not been established. However, as compared with regions in North America and the United Kingdom having hard water, in soft water areas cardiovascular deaths range from 15 percent to 76 percent higher.[19] Seelig and Heggtveitt[23] believe that the protective factor in hard water is more likely to be magnesium than calcium.

TABLE 1.—*Daily Nutritional Requirements for Magnesium*

Period of Life	*Age (years)*	*Daily Amount of Magnesium (mg/day)*
Infants	0-0.5	50
	0.5-1.0	70
Children	1-3	150
	4-6	200
	7-10	250
Males	11-14	350
	15-18	400
	19 and older	350
Females	11-14	300
	15 and older	300
	During pregnancy	300+150
	During lactation	300+150

The intake of magnesium and calcium is increased when hard water is used in cooking and as drinking water. This can make an otherwise marginal intake of Mg adequate. Theoretically, magnesium and calcium could also form insoluble soaps with saturated long-chain fatty acids and, thus, decrease the net intake of saturated fats from the diet. The solubility of these soaps is inversely related to the degree of saturation. (There is no scientific evidence for such a mechanism at this time, however.)

Actual nutritional requirements can be divided into two categories: (1) meeting the needs of normal humans for optimum nutrition and (2) meeting the needs of patients with overt or suspected magnesium deficiency to replenish the mineral until normal nutrition can be reestablished.

The 1980 recommended daily dietary allowances of the Food and Nutrition Board of National Academy of Sciences and National Research Council are recorded in Table 1.[24] These recommendations mean that a man weighing 70

kg (154 pounds) needs 5 mg per kg and a woman weighing 60 kg (132 pounds) also needs 5 mg per kg of body weight. Obviously, infants, young children and pregnant or lactating women need significantly more magnesium per day. Persons who weigh more than ideal weight eat more food and increase their intake of magnesium unless they eat mostly empty calories. Therefore, obese persons' nutritional requirements approximate the amount calculated on the basis of lean body mass. According to the magnesium content of a mixed diet (based on calculations from food table values and by chemical analysis), a diet of 2,500 kilocalories (kcal) should supply 300 mg of Mg and a diet of 3,000 kcal should supply 350 mg of this mineral. Obviously, the amount required for infants is two times or more that for adults. This permits optimum intake for rapid growth. A note of warning is needed regarding patients with chronic renal failure. The maintenance requirements are definitely less than those recommended above. It is necessary to monitor levels of magnesium from time to time in such patients.

TABLE 2.—*Causes of Magnesium (Mg) Deficiency*

Nutritional and Intestinal Causes (Inadequate Intake or Malabsorption)

- Prolonged parenteral administration of fluid, including hyperalimentation without addition of Mg for three weeks or more
- Chronic alcoholism
- Severe prolonged diarrhea, ulcerative colitis, regional enteritis, chronic laxative abuse, villous adenoma or cancer of the colon
- Intestinal Malabsorption:
  - Short bowel syndrome due to extensive resection of small bowel, jejuno-colic fistula or gastrojejuno-colic fistula
  - Gluten enteropathy (celiac disease and nontropical sprue)
  - Tropical sprue
- Starvation with attendant metabolic acidosis
- Protein-calorie malnutrition including kwashiorkor
- Diabetic ketoacidosis

Renal Causes

- Diuretics, especially furosemide and ethacrynic acid, but also thiazides
- Amphotericin B, gentamicin and gentamicin plus carbenicillin-induced renal tubular injury
- Cisplatin-induced renal tubular injury
- Renal tubular acidosis
- Recovery from acute tubular necrosis (diuretic phase)
- Chronic glomerulonephritis and pyelonephritis (rarely)
- Familial and sporadic renal wastage of magnesium

Neonatal and Childhood-Associated Conditions

- Infantile convulsions with hypomagnesemia and hypocalcemia
- Newborns of diabetic mothers
- Genetic (male) hypomagnesemia (specific malabsorption of Mg)
- Exchange transfusions (citrate effect)
- Congenital hypoparathyroidism
- Infant born of mother with hyperparathyroidism

Endocrine and Metabolic Causes

- Primary and secondary aldosteronism
- Hyperthyroidism
- Hyperparathyroidism with osteitis fibrosa cystica (particularly after parathyroidectomy)
- Malacic bone disease (usually malignant lesions)
- Excessive lactation
- Last trimester of pregnancy

Magnesium Therapy and Supplementation

More magnesium is needed during periods of stress. Pregnant and lactating women need an additional intake of about 50 percent or more than the usual adult requirement. In one case, a lactating mother, who acted as a wet nurse as well as nursing her own child, produced a total of 2,400 ml of milk per day; tetany developed. Her serum magnesium level was 0.4 mEq per liter.[25] This extreme example highlights the clear need for greater intake of Mg during lactation.

The nutritional needs of patients vary according to the nature of the illness. Often magnesium is given for a short period to provide relief of symptoms; other times, continuing Mg supplementation may be needed if the illness is expected to be prolonged. Some of the special needs of patients with certain illnesses will be discussed below. Table 2 lists common and uncommon causes of overt magnesium deficiency to point out the variety of conditions in which there may be need for Mg therapy or supplementation.

Diabetes mellitus without acidosis results in loss of magnesium, thereby causing lowering of levels of serum Mg.[26] Diabetic ketoacidosis[27] is a state of acute starvation in a patient who may already be mildly depleted of magnesium before the onset of the ketoacidosis. The Mg deficit is usually moderate and may not require special therapy, but occasionally a severe deficit results and should be corrected by parenteral administration of magnesium. Patients with diabetes mellitus should receive more Mg daily than nondiabetic

subjects. Starvation was found to be associated with hypomagnesemia after World War II.[28] Total starvation leads to a continuous loss of Mg along with other nutrients including nitrogen and phosphate.[29] Vitamins and trace elements are also lost during starvation. The sudden termination of starvation by feeding protein and carbohydrate without cofactors can result in serious metabolic and neurological disturbances in spite of supplying therapeutic doses of the needed vitamins. Starvation victims of World War II who were fed too rapidly died, but the causative factors were not determined. Florid neuropathy occurs in some severely malnourished persons on refeeding even if thiamine is supplied.[30] Because of these clinical observations, Zieve[31] studied the problem and showed that magnesium deficiency in rats impairs the transketolase activity of the liver and of erythrocytes. In rats with both thiamine and Mg deficiency, thiamine repletion resulted in half as much increase in liver transketolase activity as during simple thiamine deficiency. The evidence is good that Mg deficiency interferes with the body being able to utilize thiamine. This observation is important in treating alcoholic patients in whom thiamine and Mg are severely depleted, such as those who have signs of the Wernicke-Korsakoff syndrome.

Serious Mg deficiency occurs in protein-calorie malnutrition of young children with marasmus or kwashiorkor in tropical areas primarily, but also in any region where severe malnutrition exists.[32-34] Patients who failed to respond to protein feeding and died were thought to have irreversible biochemical and pathological changes. Caddell ascribed this to Mg deficiency. Recovery is enhanced by addition of the mineral in large amounts.[33-37] Normally nourished and growing children require large intakes of magnesium. Therefore, in children with severe protein-calorie malnutrition, the need for replenishment to permit growth is even greater. It takes many days to correct the deficit.[37]

A magnesium infusion test, also called the Mg load test, has been used in infants to determine the presence of Mg deficiency, particularly in those in whom serum Mg levels are not very low.[34,36a,b] A 40-hour test was used to study magnesium and creatinine excretion before and after an intramuscular load of 0.49 mEq of magnesium per kg of body weight. No circadian variation of Mg excretion was detected, so a preload period of eight hours sufficed for baseline. Most of the excess magnesium was excreted by neonates by 32 hours and by infants from 1 to 6 months of age within 24 hours. Retention of 40 percent or more of the administered mineral was considered significant evidence of Mg deficiency. While this is an arbitrary determination, it is consistent with clinical observations.

Severe chronic alcoholism can be considered to be a form of adult starvation because empty calories have been taken in the form of alcoholic beverages instead of substantial food. The condition of these patients is similar to that of starved persons with regards to depletion of magnesium and other elements. Alcohol enhances the loss of Mg in the urine, so that intake of nutrients other than alcohol is interrupted and a renal loss results.[38-40] Several studies of electrolytes in muscles of chronic alcoholic patients or animals show significant depletion of magnesium, potassium and phosphate.[41,42] When refeeding takes place, Mg is retained avidly for six to ten days, after which equilibrium is usually reestablished. In persons unable to eat or who have pronounced Mg deficiency, parenteral administration of Mg is indicated.[43] Magnesium deficiency occurs regularly in chronic alcoholism, but its role in the development of symptoms is still an unsettled question. Clearly, magnesium should be administered parenterally if there is associated Mg-dependent hypocalcemia, cardiac arrhythmias or convulsions. I believe that parenteral Mg administration also is indicated in patients with Wernicke-Korsakoff syndrome and delirium tremens. After recovery, simple maintenance of a well-balanced, nutritious diet is sufficient.

Malabsorption and chronic diarrhea (from any cause) are the next most common medical causes of magnesium deficiency. These conditions include the short bowel syndrome, the closed loop syndrome, chronic ulcerative colitis and colon tumors that cause diarrhea.[44-46] As with most diseases, correction of the defect—in this case malabsorption or diarrhea—results in ending the wastage of Mg and the need for Mg supplementation. Ordinarily, in patients with the short bowel syndrome only partial correction of the condition is possible; thus, continued Mg supplementation will be necessary. The limiting factor of Mg therapy is diarrhea, which results from taking the mineral orally. Thus, when oral therapy does not suffice, often it is necessary to give Mg salts parenterally by the intramuscular route; occasionally, however, they must be administered intravenously at frequent

TABLE 3.—*Guidelines for Treatment of Magnesium (Mg) Deficiency*

1. It is important to determine that the kidneys are producing urine and that blood urea nitrogen and creatinine values are normal. Magnesium may be needed and may be administered even in the presence of severe renal insufficiency, but the treatment must be monitored by measuring serum or plasma levels frequently. Note that $MgSO_4$ (magnesium sulfate) is the heptahydrate $MgSO_4.7H_2O$. Ampules containing 1.0 gram of $MgSO_4$ or 8.1 mEq of magnesium are convenient to use. Parenterally given Mg doses recommended below refer to $MgSO_4$.

   General requirements: On the first day of therapy at least 1 mEq of Mg per kg of body weight (lean body mass) should be given parenterally. Subsequently, at least 0.5 mEq of Mg per kg of body weight per day should be given for three to five days. If parenteral fluid therapy continues after this, at least 0.1 mEq per kg per day should be given. Infants and young children need twice as much.

2. The following schedule for an average adult is safe and effective.

   Intramuscular route:
   - Day 1. 2.0 grams (16.3 mEq) every four hours for five doses.
   - Days 2-5. 1.0 gram (8.1 mEq) every six hours.

   Intravenous route (this is the preferred route if intravenous infusion is being used already):
   - Day 1. 5 grams (41 mEq) per liter of fluid and at least two liters or 82 mEq.
   - Days 2-5. A total of 6 grams (49 mEq) distributed equally in total fluids of the day.

3. For a sudden emergency such as convulsions or tachyarrhythmia.*

   Intravenous dose: 2 grams of $MgSO_4$ as 20 percent solution (10 ml of 20 percent $MgSO_4$) given in one minute. This should be followed by 5 grams of $MgSO_4$ in 500 ml solution over five to six hours and, finally, followed with the intramuscular schedule for days 2-5 as listed above.

4. Oral therapy. Most Mg salts can cause diarrhea, which can be a limiting factor (other preparations than the ones listed below can also be used).
   - Liquid milk of magnesia: one teaspoonful four times a day as tolerated, or
   - Magnesium hydroxide tablets: 300 mg tablet four times a day as tolerated; increase to two tablets four times a day as tolerated, or
   - Magnesium acetate (9.35 mEq per gram) as 10 percent solution: 10 ml in water four times a day as tolerated.

5. Monitor therapy. Magnesium repletion of tissues is slow. Magnesium levels need to be checked from time to time. As satisfactory blood levels are obtained, the dose can be adjusted to the lowest dose needed to maintain normal levels. Obviously, therapy should be stopped if the acute episode that caused the disturbance in first place has been corrected. Under certain circumstances, such as renal or gastrointestinal wasting of magnesium, the oral dose should be continued indefinitely.

*Adapted from Iseri.[63]

enough intervals to prevent overt symptoms of deficiency.

In adults the use of a magnesium load test has also been found to be useful in determining the presence of Mg deficiency. Although there is a circadian variation of magnesium excretion in normal subjects, this is not of sufficient magnitude to interfere with the use of a six-hour preload determination for basal Mg excretion. An intravenous injection of 33 mEq of Mg (4 grams of $MgSO_4$) in 1,000 ml of 5 percent glucose in water is given over six hours. All urine is collected for 36 hours, including during the period of infusion. Normal persons excrete all of the magnesium injected. More than 20 percent retention is considered to be clear evidence of deficiency.[41] Thoren[44] has described using a 24-hour urine collection and considers 20 percent to 25 percent retention of injected Mg to be evidence of a deficiency.

Certain renal diseases result in wastage of magnesium. Renal tubular acidosis, which also results in potassium and phosphate wastage is associated with Mg deficit. Rarely, patients are unable to conserve Mg, resulting in clinical manifestations such as intermittent convulsions, hypocalcemia and disturbed psyche. Siblings have been reported with chronic metabolic alkalosis and hypomagnesemia due to renal wastage of magnesium and potassium.[47] A male patient was discovered to have pronounced hypomagnesemia because of convulsions at age 5. He has been followed for several years now and can be kept reasonably asymptomatic, though hypomagnesemic, by administration of 100 mEq of Mg acetate per day. He excretes more than 30 mEq of Mg a day, indicating severe renal wastage of the mineral (W. E. Klingberg and E. B. Flink, unpublished data 1968). In rare cases, a male infant or a young male child has a defect of intestinal absorption of Mg. These children also have Mg-dependent hypocalcemia. This condition usually resolves itself with time.[48]

Administration of drugs to treat various diseases often results in Mg wastage and deficiency, which necessitates the additional intake of Mg. These drugs include amphotericin B, furosemide, ethacrynic acid, thiazide diuretics (to a lesser extent), gentamicin, carbenicillin[43] and cisplatin.[49] Cisplatin may cause damage to rental tubules, which persists long after cessation of therapy.[49] The loss may occur at a time when illness prevents the patient from receiving nutritious food as the

condition worsens. Prevention of a deficit is possible by prescribing oral Mg supplements in the amount that the patient can tolerate; often, however, parenteral therapy is necessary.

Total parenteral nutrition (TPN) has become a valuable adjunct for the management of critically ill patients who are otherwise deprived of nutrition. A need for potassium was assumed and this mineral incorporated into initial solutions. It was soon discovered, however, that magnesium had to be part of the daily infusion mixture as well, or signs and symptoms of Mg deficiency occurred within three to four weeks. Previously, it was felt that healthy persons not under abnormal stress could tolerate the absence of Mg for a longer period, but not for more than four to six weeks. Development of overt signs and symptoms means that considerable loss has already occurred. The serious consequences of phosphate depletion became apparent early in the last decade.[50] To prevent Mg deficiency in TPN-treated patients at least 8 mEq should be administered in infusion mixtures per day in an adult, beginning on the first day of treatment. In infants and young children the need is twice that for adults, or 0.2 to 0.3 mEq per kg of body weight per day for maintenance. Magnesium, potassium and phosphate often are depleted under the same circumstances of illness. Magnesium deficiency increases and perpetuates potassium deficiency in spite of adequate potassium intake.[51,52] Mg deficiency also enhances phosphate loss and deficiency.[41] Therefore, Mg is essential to insure retention of these other nutrients.

The nutritional needs of patients who are Mg-deficient already and who are acutely or chronically ill often can be met only by intensive therapy. Table 3 contains guidelines and useful suggestions for administration by parenteral and enteral routes.

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Sudden Death

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *At this time of the year we invite our Chief Medical Residents to present Medical Grand Rounds. This gives us a chance to express as an academic community our gratitude to them for the superb leadership which they have brought to our patient care and teaching program during the past year. Dr. Alan Guerci will discuss the topic of sudden death.*

DR. GUERCI:† As many as 400,000 Americans will die suddenly in 1980.[1] This figure accounts for at least half of all deaths due to coronary artery disease.[2,3] This paper summarizes our current understanding of the cause and pathogenesis of sudden death and reviews efforts to identify and treat persons at risk.

Etiology and Pathogenesis

There is no universally accepted definition of sudden death. Although most investigators define it as an unexpected, nontraumatic death occurring within an hour of the onset of symptoms, definitions vary from instantaneous death to death within 24 hours. While these semantic problems occasionally confuse analyses of attempts to prevent sudden death, they should not interfere with appreciation of the basic pathophysiology. In the overwhelming majority of cases, sudden death is the result of advanced coronary artery disease (Table 1).

Kuller and co-workers[4,5] found that when sudden death was defined as death within 24 hours, approximately 60 percent of cases could be attributed to coronary artery disease. Among men aged 40 to 65, when death occurred within two hours of the onset of symptoms, coronary artery disease accounted for 85 percent. In a review of more than 1,300 autopsies, Spain and colleagues[6] concluded that 91 percent of deaths occurring within an hour of onset of symptoms were caused by coronary artery disease.

Coronary atherosclerosis in sudden death victims is characteristically widespread and advanced. Perper and colleagues[7] reported that 61 percent of 148 sudden death victims had greater than 75 percent stenosis in all three major coronary arteries. Of the 148 victims, 73 percent had at least one 90 percent occlusion; only 9 percent had no significant lesion. In a study of 87 cases of sudden death, only 8 percent had insignificant disease and only 8 percent had single-vessel disease; the remainder had multivessel stenoses, observations in keeping with earlier reports.[9]

Extensive coronary disease has also been

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ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
DPH = diphenylhydantoin
VPC = ventricular premature contractions

noted in persons resuscitated from sudden death. Weaver and co-workers[10] carried out coronary angiography in 64 sudden death survivors. Of these, 94 percent had stenosis of at least 70 percent in one vessel and 67 percent had one or more total occlusions.[10] Grove and colleagues reported virtually identical findings in a study of 55 survivors of sudden death. Of this group only 10 percent had single-vessel disease, the remainder had multivessel involvement.[11]

An intriguing and consistent observation which has emerged from studies of the pathology of the heart in cases of sudden death is that not all victims have sustained myocardial infarction. A substantial percentage of victims have neither an acute occlusion nor a recent infarction (Table 2). Indeed, most authorities on the subject place the figure for acute coronary occlusion in sudden death at only 15 percent to 30 percent.[8,15] Figures cited for fresh infarction are only slightly higher.

Small-vessel platelet aggregates have also been observed in the coronary arterioles of sudden death victims[14,15] and in an experimental animal model. Jorgensen and co-workers[16] produced immediate ST segment elevations, myocardial infarction and, in some cases, ventricular fibrillation by infusing adenosine diphosphate (ADP), a potent platelet-aggregating agent, directly into the coronary arteries of pigs. These changes could be prevented by making the animals thrombocytopenic before infusion of ADP. The therapeutic implications of these observations have been obscured, however, by the finding of platelet aggregates in the hearts of patients dying of other causes.[14,15] Whether platelet aggregation plays a causative role in sudden death or is merely an agonal event is unclear.

The absence of demonstrable myocardial necrosis in most persons dying suddenly and the realization that most inhospital sudden cardiac deaths are due to arrhythmias aroused suspicion that ventricular fibrillation is the actual physiological mechanism in most cases of sudden death not occurring in hospital. On-the-scene resuscitation efforts[8,9,17-20] and at least two cases of sudden death recorded during outpatient ambulatory monitoring[21,22] have confirmed such thinking. Asystole, the ultimate expression of cardiac entropy, is frequently observed, too, but declines in proportion to ventricular fibrillation as time from the moment of cardiac arrest to initial monitoring decreases.[9] Electromechanical dissociation, idioventricular rhythms, and supraventricular bradyarrhythmias are seen less often.

Complete heart block is seldom the cause of sudden death.[9] This observation is in accord with studies of the natural history of chronic bifascicular block.[23-25] Most such patients remain stable over relatively long periods of time. When death does occur, it is generally the result of ventricular tachyarrhythmias, recurrent myocardial infarction or miscellaneous causes other than complete atrioventricular block. In keeping with the natural history studies, follow-up studies of patients with chronic bifascicular block in whom pacemakers have been inserted for prophylaxis of transient neurological symptoms from presumed or documented bradyarrhythmias have shown a reduction

TABLE 1.—*Common Causes of Sudden Death in Adults*

Atherosclerotic coronary artery disease*
Coronary artery spasm
Coronary artery embolism
Valvular heart disease, especially aortic stenosis and mitral valve prolapse
Cardiomyopathy, including idiopathic hypertrophic osteoarthropathy
Myocarditis
Wolff-Parkinson-White syndrome
Prolonged QT syndrome, with or without congenital deafness
Complete atrioventricular block, with ischemic, degenerative, or infiltrative disease of the conduction system
Cardiac tumors
Drug toxicity (for example, quinidine syncope)
Aortic dissection/rupture
Stroke, especially intracranial hemorrhage
Pulmonary embolism

*The majority of cases of sudden death result from atherosclerotic coronary artery disease.

TABLE 2.—*Coronary Artery Occlusions and Pathology of the Myocardium in Victims of Sudden Cardiac Death*

	Friedman[12]	*Lie*[13]	*Reichenbach*[8]	*Bashe*[14]
Number of cases	25	120	87	121
Definition of sudden death	<30 sec	<6 hr	<12 hr	<24 hr
Acute occlusion	4%	17%	10%	22%
Myocardial infarction				
Recent	0	33%	26%	31%
Old	56%	41%	57%	60%
None	44%	..	33%	30%

in dizziness and syncope, but no impact on sudden death.[26]

Mounting evidence that ventricular fibrillation is the mechanism of sudden death in most patients with acute and chronic heart disease, and early reports that ventricular premature contractions (VPC's) are premonitory signs of ventricular tachyarrhythmias in coronary care units,[27] have focused attention on the VPC as a marker of susceptibility to sudden death. Several epidemiologic studies suggest that in cases of chronic coronary artery disease, advanced grades of VPC's signal an increased risk of sudden death. In a six-year study of more than 5,000 adults, Chiang and co-workers[28] found that one or more VPC's on a routine 12-lead electrocardiogram were associated with clinical evidence of coronary artery disease and with an increase in sudden death. On the basis of six-hour ambulatory monitoring, Hinkle and colleagues[29] found a correlation between VPC's, coronary disease and late mortality. The data of Rodstein and colleagues[30] also suggest a link between VPC's and sudden death in patients with heart disease.

Follow-up studies of patients who have recovered from myocardial infarction have established conclusively that patients with ischemic heart disease and advanced grades of VPC's are at increased risk of sudden death. Ventricular premature contractions on 12-lead electrocardiograms obtained from over 2,000 placebo-treated survivors of infarction in the Coronary Drug Project were associated with a twofold increase of sudden death during three years of follow-up ($P < 0.01$).[31] In another study a greater than fivefold increase ($P < 0.07$) in sudden death was noted among 160 survivors of infarction who had 10 or more unifocal VPC's per hour, multifocal VPC's, or R-on-T phenomena during eight hours of ambulatory monitoring.[32] Similar results have been published by others.[33-35] Vismara and colleagues carried out ten-hour ambulatory monitoring at the time of discharge in 64 patients recovering from myocardial infarction. Complex VPC's (defined as pairs, multifocal, R-on-T, or more than five unifocal per minute) noted in patients at discharge were clearly associated with an increased risk of sudden death over the next two years.[36] In addition, VPC's in the acute phase of infarction did not correlate with either VPC's at discharge or long-term prognosis.[36,37] In what is probably the most widely cited follow-up study, Ruberman and co-workers[38] reported an almost fourfold increase in late sudden death among survivors of infarction in whom advanced grades of VPC's (multifocal, bigeminy, couplets or R-on-T) were detected during one hour of monitoring.

What is less clearly established is whether VPC's contribute independently to late mortality or are just a marker of congestive heart failure. Follow-up studies of patients with coronary artery disease consistently identify congestive heart failure as a key determinant of late mortality.[39-46] In these and other studies[47,48] it has been shown that VPC's correlate with extent of coronary artery disease and left ventricular dysfunction. Although data from Ruberman's study indicate that VPC's continue to predict late sudden death even when adjustments are made for congestive heart failure, assessments of left ventricular performance were indirect. As Schulze and colleagues[47,48] have shown, an x-ray study of the chest is a specific but not highly sensitive test of heart failure. They carried out coronary angiography, left ventriculography and technetium 99 wall motion studies in a series of infarct survivors. Complex VPC's (multifocal, pairs, salvos or more than 30 unifocals per hour) on 24-hour Holter monitoring at discharge were detected in patients with more numerous and advanced coronary stenoses and with more extensive segmental and global impairment of left ventricular function. Ejection fraction did not correlate with cardiothoracic ratio because substantial numbers of patients had minimal or no cardiomegaly on routine x-ray studies of the chest. Ejection fraction in 22 patients without complex VPC's averaged 50 percent, and only eight patients in this group had ejection fraction of less than 40 percent. On the other hand, 13 of 14 patients with advanced grades of VPC's had an ejection fraction of less than 40 percent, and the mean for this group was 31 percent.

In a subsequent study,[49] it was shown that VPC's probably contribute to sudden death independently of congestive heart failure. Of 45 survivors of infarction with an ejection fraction of less than 40 percent, 26 were found to have complex VPC's at the time of discharge. Eight died suddenly during the next year. Of the 19 patients with ejection fraction of less than 40 percent but no complex VPC's, none died ($P < 0.02$).

Selection of Patients for Therapy

Congestive heart failure increases late mortality among survivors of myocardial infarction. Such

patients will be treated for symptoms of heart failure irrespective of prognosis. If, as seems to be the case, VPC's are an independent risk factor for sudden death in patients with coronary artery disease, then it becomes necessary to select patients for therapy. Whom to treat is the first in a series of perplexing questions.

Much has been written about the prodrome of sudden death; perhaps the patients can warn their physicians of impending disaster. After all, several studies have shown that roughly 30 percent of sudden death victims seek medical attention in the month before death.[2,12] Unfortunately, their complaints are usually so nonspecific as to lack therapeutic implication. For example, undue fatigue is probably the most frequently mentioned problem. An additional 20 percent to 25 percent of sudden death victims never express complaints referable to their cardiovascular systems; they die without previous history of heart disease.

Vague as it seems, the complaint of undue fatigue is extremely interesting when viewed in light of experimental evidence that psychological stress lowers the ventricular fibrillation threshold in normal and acutely infarcted animals, that psychological stress can provoke ventricular fibrillation in otherwise stable, acutely infarcted animals, and that beta-adrenergic blockade can prevent the adverse effects of stress in these situations.[50] Application of these findings to individual patients in a quantifiable fashion remains difficult, however.[51,52]

Clearly, patients cannot select themselves for therapy. Is it reasonable to treat all survivors of myocardial infarction? They have already manifested their coronary artery disease, and they constitute a much more readily identifiable group than those with asymptomatic coronary artery disease. Several efforts have been made along these lines using three classes of drugs: the antiarrhythmic drug diphenylhydantoin (DPH), the antiplatelet agents acetylsalicylic acid and sulfinpyrazone (Anturane), and beta-adrenergic antagonists.

In a single-blind prospective study of survivors of infarction under the age of 70, more than 500 patients were treated with 100 mg of DPH either three times or four times a day, or with a placebo.[53] At the end of one year, death rates were the same (approximately 10 percent) in treated and control groups. However, in one cooperating hospital, DPH levels were measured and 10 deaths were noted among 64 patients with average levels of less than 10 μg per ml. There were no deaths in 32 patients with levels of more than 10 μg per ml. A second randomized study was therefore undertaken. The treatment group were given doses of DPH adjusted to maintain levels above 10 μg per ml. Death rates at one year were 12 percent in the treatment group versus 14 percent in the control group (difference not significant).[54] On the basis of these data, there is no justification for prophylactic administration of DPH to survivors of myocardial infarction.

Several large trials using acetylsalicylic acid have failed to reduce late sudden death among infarct survivors. Elwood and Sweetnam[55] gave 300 mg of acetylsalicylic acid three times a day to half of 1,682 infarct survivors. As with an earlier study,[56] there was no significant impact on mortality at one year. Another multicenter study enrolled 4,524 patients eight weeks to five years after infarction for treatment with either 500 mg of acetylsalicylic acid twice a day or a placebo. No differences were observed in the incidence of late sudden death, recurrent myocardial infarction or total mortality.[57]

These investigations have been criticized because of frequent late entry of patients and because of the doses of acetylsalicylic acid involved. Late entry is an important consideration because it is known that the highest postinfarction death rates occur in the first 6 to 12 months of convalescence. Patients enrolled after this time represent a select group of survivors of infarction. However, Elwood and Sweetnam[55] began treatment of patients a week after infarction in their second trial. The Aspirin Myocardial Infarction Research Group analyzed data separately for patients enrolled eight weeks to six months after infarction and still found no benefit. The dose controversy revolves around the observation that synthesis of thromboxane A_2, a potent vasoconstrictor and platelet-aggregating agent, is inhibited by lower doses of acetylsalicylic acid than are necessary to block formation of prostacyclin, a vasodilator produced by vascular endothelium. Ideally, the dose of acetylsalicylic acid should be regulated to preferentially inhibit synthesis of thromboxane A_2. However, in the doses given, this drug is capable of suppressing both. Whether a lower dose would have provided benefit is conjectural.[58] The fact remains that available data do not support the assertion that this drug can reduce late sudden death among survivors of myocardial infarction.

In a widely hailed study of 1,475 patients, the

antiplatelet drug sulfinpyrazone (Anturane) was found to reduce sudden death by approximately 70 percent when taken in the first six months after infarction.[59] However, on April 25, 1980, the Food and Drug Administration (FDA) withdrew approval for the use of sulfinpyrazone for this purpose.[60] The FDA has disputed a number of exclusions (for minor protocol violations) of treated patients who later died suddenly. In addition, the FDA argues that more detailed examinations have shown that many of the placebo-treated patients initially labeled as having died suddenly in fact died of recurrent infarction or other causes. Reclassification of deaths according to FDA criteria showed a modest but statistically insignificant benefit from sulfinpyrazone.

Several randomized prospective trials have shown that in suitable candidates (such as those without severe congestive heart failure, obstructive lung disease or atrioventricular block), beta-adrenergic blockade can reduce late sudden death among infarct survivors. In a study of more than 3,000 patients, practolol reduced sudden death by 40 percent ($P < 0.02$) but produced an unacceptable rate of side effects.[61] Wilhelmsson,[62] Ahlmark,[63] and their colleagues reported more than 75 percent reduction in sudden death among patients treated with alprenolol for two years ($P < 0.05$). Total cardiac deaths were also reduced in the alprenolol-treated group, but the difference failed to reach statistical significance. Anderson and co-workers reported a 50 percent reduction in mortality among survivors of infarction who were treated with alprenolol.[64] However, sudden death was not analyzed as a separate end point. Neither of these drugs is available in this country. A multicenter trial of propranolol involving more than 4,000 patients is currently under way, but results will not be available for two or three years. Even if this study confirms the earlier reports, its application will be limited because patients with severe congestive heart failure, known to be at high risk for late sudden death, must be excluded from therapy.

Efforts have been made to identify subpopulations of infarct survivors at high risk for late mortality. For the most part, these efforts have lacked direct bearing on the problem of sudden death. Multivariate analysis of clinical and electrocardiographic features of acute myocardial infarctions have been used to estimate long-term prognosis, but these formulas have defined total mortality, not sudden death, as the end point. At an even more fundamental level, these schemes are flawed by lack of proven validity when applied to populations other than the ones from which the original analyses were made (for example, infarctions treated at referral versus community hospitals). However, a promising indication is ST depression during treadmill testing at the time of discharge. Although several studies[65-67] indicate that exercise testing can predict late cardiac "events," few of those events have been sudden death. Meaningful analysis with regards to predictive value for sudden death is therefore difficult. Applicability of this technique to the problem of sudden death is further limited by the fact that only patients with relatively uncomplicated infarctions have been studied.

Two groups of patients are particularly vulnerable to late sudden death. The first are persons resuscitated from ventricular fibrillation who have not sustained a myocardial infarction with their episode of aborted sudden death. And, as has already been mentioned, ventricular arrhythmias in the acute phase of myocardial infarction do not correlate with arrhythmias in the convalescent phase or with late prognosis.[37] This rule includes even ventricular tachycardia and fibrillation in cases of acute infarction, neither of which adversely affects long-term survival.[19,68] However, several studies show that survivors of sudden death without infarction carry a dismal prognosis. Liberthson and co-workers[17] found that in 27 such patients the sudden death recurrence rate at one year was almost 30 percent. Cobb and associates[19] also found a recurrence rate of about 30 percent in this group of patients, with a median time to recurrence of only five months. Customary doses of conventional antiarrhythmic drugs were given by local physicians in most cases but failed to produce any beneficial effect.

Treatment for these patients remains problematic. In one study[69] 16 sudden death survivors were treated with high doses of quinidine (1.6 to 3 grams per day) or procainamide (2 to 5 grams per day) to maintain trough levels at 4 to 8 μg per ml and 3 to 6 μg per ml, respectively. Monthly Holter monitoring documented advanced grades of VPC's in 75 percent of the patients. One year survival was 94 percent. There was neither baseline pretreatment Holter monitoring to determine if antiarrhythmic therapy reduced ventricular ectopy nor a control group.

In an uncontrolled study 90 percent survival at

17 months was reported in a small group of patients resuscitated from out-of-hospital ventricular fibrillation.[70] A protocol was used in which antiarrhythmic efficacy, defined as abolition of pairs, runs, or R-on-T VPC's and 50 percent supression of all VPC's, was determined during ambulatory monitoring, exercise and psychologic stress testing. The authors do not clearly state the percentage of survivors of sudden death in whom their protocol can provoke complex ventricular ectopy. This is an important problem, because such patients occasionally do not have complex VPC's during ordinary activity. A more serious drawback is the time required for completion of their protocol. Patients are kept in the hospital for an average of two to three weeks before a satisfactory drug combination is found.

Limited data are available on the use of right-sided heart catheterization and programmed ventricular stimulation in the selection of antiarrhythmic therapy for survivors of sudden death without myocardial infarction. While ventricular tachycardia can be induced with critically timed electrical stimulation of the ventricle in the overwhelming majority of patients with chronic recurrent ventricular tachycardia, available information suggests that attempts at arrhythmia induction are less often successful in sudden death survivors.[71,72] As in chronic recurrent ventricular tachycardia,[73-75] suppression of induction with antiarrhythmic drugs seems to protect patients against recurrence, but the number of patients studied was small (15) and the follow-up period was only nine months.[76]

Finally, there are no controlled studies comparing the effectiveness of these approaches.

The second group of patients with increased vulnerability to late sudden death, one which encompasses a large portion of deaths due to ischemic heart disease, are survivors of infarction with advanced grades of VPC's. Evaluation and treatment of this group is an extremely perplexing problem. Using a variation of programmed ventricular stimulation, Greene and co-workers[77] provoked repetitive ventricular systoles in a group of infarct survivors. Patients with the repetitive ventricular response had a high incidence of late sudden death, and suppression of the repetitive ventricular response in patients with recurrent ventricular tachycardia favorably influenced survival.[78] However, the sensitivity and specificity of this technique have come under question. Mason[79] has been unable to induce repetitive ventricular responses in patients with chronic coronary disease complicated by ventricular tachycardia, and Josephson and colleagues[80] have been able to provoke it in normal subjects. Despite its sound theoretical basis,[81] repetitive ventricular response testing has been largely abandoned.

Coronary artery bypass operations have not been employed in a randomized prospective fashion in patients known to be at high risk for sudden death. Despite encouraging reports from uncontrolled studies,[82,83] the procedure is not generally favored.[84] Early enthusiasm notwithstanding, the procedure has been proved inadequate for patients with recurrent ventricular tachycardia.[85,86] Available evidence does not support recommendation of bypass operations for routine prophylaxis of sudden death in patients with coronary disease.

What remains are two unassailable and unavoidable facts. On one hand, survivors of infarctions with frequent VPC's have increased risk of late sudden death. On the other, there is no proof that conventional antiarrhythmic drugs in usual (or any other) doses can prevent these deaths. To invoke the obvious need for further investigation does not solve the dilemma confronting patients and physicians alike. Two recommendations can be made. First, all infarct survivors should probably have 8 to 24 hours of ambulatory monitoring at the time of discharge. At the very least, those without complex arrhythmias can be identified. Second, extrapolation from the data of Lown and Myerburg obliges efforts either to suppress ventricular ectopic activity[87] or to ensure adequate drug levels.

Conclusion

Most cases of sudden death are caused by ventricular fibrillation complicating advanced coronary artery disease. Ventricular premature contractions and congestive failure are independent risk factors for sudden death in patients with ischemic heart disease. While antiplatelet agents have not been shown to improve the prognosis of survivors of infarction, beta-adrenergic blockade seems to reduce sudden death rates in survivors with minimal or no heart failure. Conventional antiarrhythmic therapy is clearly inadequate in survivors of sudden death who have not sustained myocardial infarction. Treatment for this group and for survivors of infarction with complex VPC's at discharge remains problematic. Better ways of

evaluating the electrical stability of the ventricles and controlled trials of drug intervention are needed.

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Important Advances in Clinical Medicine

Epitomes of Progress — Otolaryngology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in otolaryngology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in otolaryngology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Computed Tomography With Simultaneous Contrast Sialography

CONTRAST SIALOGRAPHY is most useful in investigating radiolucent calculi and chronic inflammatory diseases to detect or exclude duct stricture or sialectasis. Sialography is of limited value in investigating mass lesions. In general, if the mass is intrinsic and at least 1 cm, it will distort the duct system enough to allow its identification. Others feel sialography is useless in the evaluation of mass lesions because the results cannot provide clinical data needed to determine whether the mass is a neoplasm or whether it is benign or malignant.

Computed tomography (CT) has not proved useful in the evaluation of mass lesions of the parotid gland. However, CT scanning can be combined with simultaneous contrast sialography. This technique involves doing a standard sialogram using meglumine diatrizoate as the contrast medium while the patient is inside the scanner. The patient injects the medium himself and is instructed to inject to the point of discomfort. Scans are then taken 0.5 to 1.0 cm apart, starting at the level of the zygomatic arch. This increases the roentgenographic density of the duct system and parenchyma.

The combined technique has several advantages over other methods of investigation. (1) It can detect intraparotid masses before they are palpable. In our early work with this technique, bilateral studies were done. In one patient a mass was noted on the "normal" side, which became palpable two weeks later. (2) It can show small masses superimposed on the parotid. In one patient a 0.5-cm mass was detected lying on the lateral surface of the gland. This was treated with the expectation that it was a periparotid node and it disappeared subsequently. (3) It can clearly delineate masses medial to the parotid. In several patients this technique has been able to separate deep lobe tumors from other parapharyngeal masses. (4) Because of the axial projection, it shows the relationship of the parotid tumor to the styloid process, the mastoid tip and the facial nerve. (5) Further, it has been able to accurately show extraparotid extension of malignant parotid lesions. In the first malignant lesion scanned by the authors, the tomograms detected the clinically unsuspected invasion of the sternocleido-mastoid muscle. This was confirmed at operation.

Thus, computed tomography combined with simultaneous contrast sialography increases the

radiodensity of the normal parotid gland sufficiently to allow easy separation of normal parotid tissue from intrinsic masses and from extrinsic medial or lateral masses. Further, it clearly delineates the proximity of the mass to the styloid process and the mastoid tip and, thus, the facial nerve.

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The Glycerin Test for Meniere Disease

THE TRADITIONAL DIAGNOSIS of Meniere* disease has been based on an appropriate history of tinnitus, vertigo, and fluctuant hearing loss, and on negative findings of physical examination, laboratory tests and radiological studies regarding mass lesions of the cerebellopontine angle. At present, the accepted definition of the disease by the American Academy of Otolaryngology recognizes two subvariants: one without vertigo (cochlear hydrops or endolymphatic hydrops) and one without hearing loss (vestibular hydrops).

The glycerin test specifically diagnoses cochlear hydrops and recently has been used in a large series of cases in Italy, Sweden and the United States. It is a test that uniquely combines medical and audiological techniques to permit a rapid diagnosis in most cases.

The excessive intraocular pressure found in patients with glaucoma is analogous to the problem of cochlear hydrops in Meniere disease. Just as glycerin reduces pressure within the eye, when administered as an osmotic agent, it reduces the excessive fluid of the inner ear system and improves hearing. Angelborg and Agerup proved the fundamental hypothesis of the test by showing that glycerin (administered to guinea pigs) reduces intracochlear pressure.

A detailed test protocol and reports of extensive use of the test in the Department of Otolaryngology at the University of Washington have been published by the author. A weight-related dose of glycerin mixed with grapefruit juice was given to patients by mouth, with hearing measurements made immediately before the test and three hours following it. Dramatic improvement in pure-tone thresholds or speech discrimination function, or both, indicated a positive response in 70 percent of patients with a final diagnosis of Meniere disease associated with cochlear hydrops. Side effects from the test are within acceptable limits and false-positive responses are not significant. Recent reports by Arenberg and others have suggested that a positive test result provides a favorable prognosis for surgical treatment of Meniere disease by endolymphatic sac procedures.

The glycerin test is objective and may serve as a guideline to determine whether more extensive, costly and invasive diagnostic techniques are needed. It is suitable as a routine office procedure.

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Irradiated Cartilage in Head and Neck Reconstruction

FOR MANY YEARS several reconstructive surgeons in Europe have used irradiated cartilage from cadavers for the reconstruction of facial defects. This material has been used sporadically by a handful of surgeons in the United States. Its limited use may be due to surgeons' fear of graft rejection or the lack of a readily available and suitable source of irradiation for the implants.

The method of cartilage preparation generally used has been described by Dingman. Costal cartilage is taken from cadavers of persons under the age of 40, who have died from neither a malignant condition nor sepsis. Under clean conditions, each piece of cartilage is submerged in a sterile saline solution in a mason jar. The lid is screwed down tightly and taped in place to ensure an airtight seal. The cartilage is exposed to a powerful source of gamma irradiation, such as that produced by an atomic pile, and a dose of 6 to 10 million rads is delivered. A gamma source of radiation is essential because other sources may

*THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

render the graft material radioactive. The jars are then stored at room temperature. The shelf life is at least two years. The irradiation not only sterilizes the cartilage but also appears to render it immunologically inert. This is evidenced by the minimal absorption that occurs after implantation and the infrequency of local immunologic response. Moreover, preliminary work indicates that host chondrocytes may eventually invade the implanted tissue.

Irradiated cartilage has many uses. Over the past eight years we have used it for chin augmentation, repair of saddle-nose deformity, malar augmentation in Treacher-Collins syndrome, cranioplasty in frontal skull defects and an onlay graft in hemimandibular atrophy. It can be carved with ease and maintains its shape well. It is readily available and obviates the need for taking a hip or rib graft, with the attendant risks of unpredictable graft absorption and potential complications. Research by the author is being directed at clarifying the biological activity of irradiated cartilage.

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Argon Laser Treatment of Port-Wine Stains

THE WORD LASER is an acronym derived from the first letters of the words "light amplification by stimulated emission of radiation." The argon laser produces a blue-green beam of light which is selectively absorbed by red pigment. This characteristic of argon laser light has been successfully applied in the treatment of vascular anomalies of the skin, particularly port-wine stains. The early results of Apfelberg, Maser and Lash have been duplicated by several authors.

Unlike carbon dioxide lasers, argon lasers spare epithelial tissue and photocoagulate subepithelial vascular tissue with little or no scarring. Following treatment of an initial test patch, which is successful 75 percent of the time, the area of port-wine stain is treated with a 1 to 2 mm argon laser beam until the entire area of the defect is covered. Improvement in the appearance of the malformation can be expected in 60 percent to 70 percent of cases.

Laser treatment of telangectasias and hemangiomas can be done on an outpatient basis, with local or general anesthesia. Although the results in adults are satisfying, its effectiveness in children has yet to be determined. With further refinement of technique and careful patient selection, argon laser treatment will be a welcome addition to the management of patients with this deforming condition.

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Use of Pedicle Flaps in the Surgical Treatment of Alopecia

THE NEWEST PROCEDURE of surgeons doing hair replacement procedures is the Juri flap operation. In 1975 Dr. Jose Juri of Buenos Aires described his six-year experience with temporo-parieto-occipital pedicle flaps for the treatment of alopecia. The design and number of flaps depends on the location and the degree of baldness.

Each twice-delayed, 4-cm flap is pedicled on the superficial temporal artery, and is long enough to reach the fringe on the opposite side of the area of alopecia. The delays are done while the patient is under local anesthesia; however, the final transposition is carried out under general anesthesia. "Dog-ear" formation may occur at the base of the flap where it is rotated upon itself at the hairline. This can be hidden with proper hairstyling until it is revised four to six weeks later.

The main advantage of the flap is that coverage is immediate and continuous. Because the hair is never totally separated from its blood supply, there is no temporary loss of hair as occurs with hair transplantation. It is a more involved procedure, but larger amounts of hair with much greater density are transferred with this operation (the equivalent of about 350 punch grafts). In most patients, *total coverage* with normal hair density can be obtained by stretching the flaps and carrying out scalp reductions.

Another approach is the use of shorter non-

delayed flaps, 2.5 to 3.0 cm wide, taken from both sides of the scalp (each crossing half of the area of alopecia). This procedure was first described by Passot in 1919 and, more recently, by Elliott in 1977. The operation is not as extensive, and the donor areas on both sides of the scalp are used to cover an area equivalent to less than one Juri flap. This technique should be used only in patients with minimal frontal loss of hair who do not face the possibility of extensive alopecia.

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Skin Flaps and Vasodilators

SKIN FLAP VIABILITY is crucial to almost all surgeons. It is particularly important in plastic and reconstructive surgical procedures when local skin flaps are advanced, rotated or transposed. Flap necrosis can be a disaster, and is often related to an inadequate blood supply. Many tests have been devised to predict skin flap viability, the most valuable of which is administration of the dye fluorescein. After the flap is raised, 1 gram of fluorescein is given as an intravenous push. Some 20 to 30 minutes later the flap is examined with a Wood's light. If the flap shows evidence of the dye, the blood supply is adequate. However, if it is totally black, the flap is not receiving blood and will not survive. Many surgeons using large flaps, including myocutaneous flaps, carry out this test routinely.

Survival of local skin flaps can be enhanced. Flap delay has long been used, and is still felt to be useful for many large transposition flaps such as the forehead flap. Flap viability is determined by the local blood supply; hence, a variety of vasodilators have been tested, with significant results. Circulation in skin and skeletal muscles is controlled by smooth muscle sphincters. This is regulated by intrinsic and extrinsic factors and can be affected by both humoral and neural systems. Isoxsuprine (Vasodilan) is a beta-adrenergic stimulator which, in a variety of studies in animals, has been found to affect precapillary sphincters. Isoxsuprine has significantly improved flap circulation and survival, and in both animals and humans, is probably better than any other form of local vasodilation. In both experimental and clinical flaps with areas not expected to survive, based on results of fluorescein testing, significant increases in length of survival occurred following the use of isoxsuprine. This drug has been useful both in skin flaps and for myocutaneous flaps.

Finseth reported three cases in which distal portions of local skin flaps looked poor and showed no fluorescence following fluorescein testing. It was expected that the flaps would slough. However, isoxsuprine was given, and in all three cases, flap viability improved and no serious damage occurred.

If either flap viability or fluorescein angiography is in question, isoxsuprine should be administered immediately. In the operating room, 10 mg may be given parenterally, followed by the same dose administered every six hours. As soon as the patient can receive nourishment orally, 20 mg of isoxsuprine should be given every six hours for approximately ten days.

It is our policy at both the University Hospital and Veterans Administration Medical Center in San Diego to carry out fluorescein angiography in all cases of large skin flaps. If there is any question of viability, patients are begun immediately on this vasodilator regimen.

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Obstructive Sleep Apnea

OBSTRUCTIVE SLEEP APNEA (OSA) is defined as a complete cessation of nasal and oral air flow during sleep for greater than ten seconds, accompanied by persistent chest wall and abdominal movement. For almost a decade, OSA has been studied in children with pulmonary hypertension and congestive heart failure secondary to adenotonsillar hypertrophy, macroglossia or micrognathia. The more subtle clinical manifestations of the OSA syndrome are now recognized and include hypersomnolence, weight loss, behavioral disturbances and enuresis.

Previously, those children who may have bene-

fited from surgical treatment required rather complicated recordings of chest wall and abdominal movements, nasal and oral air flow, extraocular muscle movements, intraesophageal pressures and intra-arterial oxygen saturation, as well as an electroencephalogram, electrocardiogram and electromyogram.

A simple technique is now available to estimate arterial oxygen and carbon dioxide tension with continuous skin surface electrode recordings. The skin surface oxygen tension (Pso_2) and carbon dioxide tension ($PsCO_2$) closely parallel arterial oxygen and carbon dioxide tensions, with response times between 45 seconds and two minutes. Concomitant respiratory efforts can be readily detected by a trained observer. Nasal and oral air flow are easily determined by auscultation, and sleep state evaluated as active (rapid eye movements, intermittent low-amplitude movements of the extremities and irregular respiration) or quiet. The portable electrode recordings, when combined with careful clinical evaluation, eliminate the previous cumbersome sleep study protocols, and permit a rapid assessment of those patients who may benefit from surgical intervention.

Decreases in Pso_2 to 50 mm of mercury or less combined with increases in $PsCO_2$ of 45 mm of mercury or more during sleep correlate well with OSA. Following surgical correction of the mechanical obstruction, Pso_2 and $PsCO_2$ determinations should return to normal during sleep, with resolution of OSA and its more subtle clinical manifestations.

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Nasopharyngeal Carcinoma

A UNIQUE, racially balanced North American series of 209 patients with nasopharyngeal carcinoma (NPC) who were treated by primary radiation therapy was studied. Of these patients, 49 percent were Chinese and 51 percent were non-Chinese (predominantly white). Whereas Chinese born in China had a 117.9 times greater incidence of the disease (27.12 per 100,000 population per year), Chinese born in North America showed only a 7.3 times greater incidence (1.69 per 100,000 population per year) than whites (0.23 per 100,000 population per year). The five-year absolute survival with no evidence of disease (NED) was 25.6 percent for Chinese and 32 percent for non-Chinese patients. Neither this nor other racial differences were statistically significant.

The ultimate survival and prognosis of patients appeared to depend on four main factors.

(1) Histological classification of the tumor had a statistically significant effect on survival. Patients with nonkeratinizing squamous cell carcinoma had a better prognosis (31.5 percent, five-year NED) than those with keratinizing squamous cell carcinoma (16.3 percent, five-year NED). Patients with lymphoepithelioma had the best survival (52.4 percent, five-year NED). Hoppe and colleagues described a 50 percent incidence of lymphoepithelioma in their series, which partially accounts for their excellent overall survival rate.

(2) The stage of the tumor had a significant effect. The overall five-year NED survival for the series was 29 percent. When localized NCP, with or without nodes, was analyzed, the survival rate was increased to 41 percent, five-year NED.

(3) The dose of radiation given was important. Patients treated with 6,000 rads or more had a 35.7 percent, five-year NED survival, irrespective of the tumor's stage. Hoppe and colleagues used even higher doses of therapy to achieve their excellent results.

(4) A newly described factor affecting survival of patients with NPC is biopsy of nodes before irradiation. Two groups of patients with nasopharyngeal carcinoma that metastasized to the neck, and differing only in the variable of a biopsy being done before treatment, were studied. The trend toward poorer survival was consistent when biopsies of nodes in the neck were done before radiation therapy. This was most apparent in patients with mobile nodes, who had a five-year NED survival of 46.9 percent when nodes were not biopsied and 25 percent when they were. This difference approached statistical significance ($P = 0.063$), and is evidence that excision of the node before irradiation should be avoided in the management of NPC. McGuirt and McCabe reported similar findings in assessing complications seen after neck biopsy before radical neck operations.

Any patient with a suspicious node in the neck must be completely searched for a primary tumor

before excising the node. Aspiration needle biopsy should be considered as a safer alternative diagnostic procedure.

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Myocutaneous Flaps for Head and Neck Reconstruction

THE RECENT DEVELOPMENT of myocutaneous flaps has improved the success of one-stage (primary) reconstruction of extirpative defects of the head and neck. These regionally based flaps can be rotated from the neck, chest or back on branches of the thoracoacromial, external carotid arteries or thyrocervical trunk to resurface cutaneous defects of up to 12 by 20 cm. Bone from the ribs or scapula can also be incorporated as a compound osteomyocutaneous flap to reconstruct bony defects of the mandible, maxilla or skull.

The survival of any flap depends on maintaining satisfactory circulation. The cutaneous portion of the myocutaneous flap receives its blood flow by way of an anatomically recognized arteriovenous circulation that follows the long axis of the flap, on the deep surface of the muscle, ultimately providing branches to the distal dermal-subdermal plexus via perforating vessels up through the muscle. The viable length of this flap is therefore not related to its width, but rather to its intact perfusion of blood via specific axial vessels included in the flap. This is contrasted to flaps perfused in random fashion in which nutrients are derived solely from intercommunications of vessels in the dermal-subdermal plexus with those from the flap's pedicle.

Examples of regional myocutaneous flaps being used include the pectoralis major (based on the pectoral branches of the thoracoacromial artery), the trapezius (based on branches of the thyrocervical trunk, especially the transverse cervical artery), the sternocleidomastoideus (based superiorly on branches of the occipital artery, in the midportion on branches of the superior thyroid artery or inferiorly on branches of the inferior thyroid artery) and the latissimus dorsi (based on branches of the thoracodorsal artery). Where bone is required, portions of the clavicle, ribs or scapula can be incorporated. Of these, the pectoralis flap appears to be the most reliable and useful.

Flaps have been used to reconstruct the floor of the mouth, pharynx, esophagus and soft tissues of the head and neck, as well as defects in the mandible, maxilla and other portions of the skull. The donor site can often be closed primarily, but skin grafting may be required where larger "paddles" of skin are transferred. Smaller flaps can be used in women without sacrifice or significant distortion of the overlying breast tissue.

The availability, technical ease of the operation (as opposed to microvascular flap transfer which may take 9 to 14 hours to accomplish) and reliability of these flaps make them very attractive for reconstruction of a variety of sites in the head and neck region. They do not require initial delay or subsequent flap division. They tolerate radiation well and are outside the field of radiation if preoperative radiation is required, or if the procedure is required for surgical salvage of radiation failure.

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Cricothyroidotomy

AMONG THE BETTER established canons of current medical practice is avoidance of prolonged tracheal intubation via a cricothyroidotomy. This procedure has been reserved for situations of extreme airway obstruction when endotracheal intubation is impossible. It is advised that the cricothyroidotomy be converted to formal tracheotomy when the clinical situation becomes stabilized (within 24 hours).

Support for this position has its foundation in an article by Chevalier Jackson published in 1921, which condemned "high tracheotomy" in no uncertain terms. In that era, such emergency procedures were done to relieve obstruction from acute inflammatory disease of the larynx such as diphtheria and croup. Jackson's conclusion was that acute laryngeal inflammation was aggravated by the proximity of a cricothyroidotomy and resulted in chronic laryngeal stenosis. This conclu-

sion may continue to be valid in the cases of acute laryngeal inflammation.

Some surgeons suggest that elective cricothyroidotomy of today is different from the procedure Jackson condemned 60 years ago. They propose that a controlled procedure carried out with an endotracheal tube in place and in the absence of laryngeal inflammation will not result in severe laryngeal complications. Brantigan and Grow as well as others have demonstrated the probable safety of cricothyroidotomy when converting from prolonged endotracheal intubation for longer-term ventilatory management. These authors reported a very low incidence of laryngeal complications and emphasize the technical simplicity and low order of surgical complications when comparing cricothyroidotomy with tracheotomy. These studies must be criticized, however, for a lack of thorough follow-up examination of the larynx.

Although it is possible that cricothyroidotomy may have a broader application in the future, it is important to establish the incidence of laryngeal complications by prospective studies that emphasize follow-up examination of laryngeal function.

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Otitis Media and Vitamin A Deficiency

In a study of the effects of vitamin A deprivation on rats, otitis media was observed in most of the animals when signs of severe vitamin A deficiency developed. On histological examination of the temporal bones, a typical, purulent exudate was found in the middle ears and eustachian tubes of many of these animals. A detailed study of the mucosa in these areas showed that the normally pseudostratified ciliated columnar epithelium of the anterior middle ear and eustachian tube had become squamosal. Squamous metaplasia was found in all areas that normally were columnar, and foci of keratinization were visible in the eustachian tube. At no time were cholesteatomas found. It has been hypothesized that the mucociliary blanket of the middle ear and eustachian tube is disrupted by vitamin A deficiency and squamous metaplasia, and that the failure to clear the middle ear leads to infection.

It has been estimated that 25 percent of children in some parts of the world are clinically deficient in vitamin A and that 13 percent of children in lower socioeconomic groups in the United States are deficient as well. On theoretical and experimental grounds, it is reasonable to speculate that the human middle ear undergoes similar changes to those described above during vitamin A deficiency. If this is the case, vitamin A deficiency may be a significant factor in the genesis of otitis media.

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Computerized Cranial Tomography in Acoustic Tumor Diagnosis

Computerized cranial tomography (CCT) has revolutionized the diagnosis of acoustic tumors. On the basis of normal results of CCT scanning, some physicians exclude acoustic tumors from the possible diagnoses. However, an acoustic tumor may be present despite a normal CCT result. In a recent series of 237 patients with acoustic tumors studied by computerized cranial tomography (Wong and Brackmann), false-negative CCT results were found in 29 percent.

When auditory or vestibular signs or symptoms indicate the possibility of an acoustic tumor, a complete evaluation and definitive determination of the presence or absence of such a tumor are necessary. The following protocol is recommended.

Computerized cranial tomography is done after 300 ml of 30 percent iodinated contrast material is administered intravenously. Scanning begins when approximately half of the iodine solution has been administered. The computer is manipulated so that only bone density is displayed. Thus, the internal auditory canals can be identified.

The percentage of patients with acoustic tumors who are successfully identified by this technique will depend in part on the sophistication of the scanner used. Older, less sophisticated scanners usually do not permit identification of tumors smaller than 1.5 cm. This technique did not

detect 29 percent of acoustic tumors in patients in the previously mentioned series. Therefore, we recommend further studies when an acoustic tumor is suspected.

To detect smaller tumors, it is necessary to introduce a contrast material into the cerebellopontine angle. After 4 cc of oxygen is injected, the scan is repeated with the patient's head turned so that the suspected ear is in the upward position. This procedure requires a body scanner. If there is no acoustic tumor, air will fill the internal auditory canal and all but the smallest tumors will be excluded. With this technique, tumors as small as 7 mm have been identified.

However, even this technique may not detect very small tumors in the distal end of the internal auditory canal. To rule out this possibility, isophendylate (Pantopaque) is inserted into the lumbar subarachnoid space through the same needle used to inject the air. Three ml of the preparation is instilled and later introduced into the cerebellopontine angle, and polytomography of the internal auditory canals is done. Dye in the internal auditory canals rules out the possibility of an acoustic tumor. Even very small tumors in this region can be diagnosed using the polytome Pantopaque technique.

One should not depend on conventional computerized cranial tomography alone to diagnose acoustic neurinomas. Introduction of contrast material is necessary to diagnose small tumors.

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EDITORIALS

Of Elections, Majority Rule and Special Interests

MOST AMERICANS HOLD to the view that our system of government, imperfect as it may be, is the best in the world and they seldom question its workings. A keystone of this system is that the majority shall rule and that the will of the majority is expressed in local, state and national elections. The right to vote in these elections was and still is treasured. But even so, there seems to be a growing sense of apathy among many voters and a disturbing disinterest in participating in the voting process, especially among the young. Perhaps it is time to examine what seems to be happening.

A national election, and particularly a Presidential election, focuses attention on the voting process. One senses that the name of this game is to get elected and that there is a lot more to getting elected than dutifully reflecting the views of a majority of the voters. Actually the process gives only token opportunity for expression of the voters' views. The majority is largely silent and certainly inactive when compared with many special interest groups which in reality often reflect more the views of their leadership than those whom they purport to represent, that is, the silent majority. Certainly the process of selecting candidates for President and other high public offices gives precious little attention to the issues that may concern the public. Even on election day the issues still take second place because most of them are not on the ballot. Restricted to voting for the candidates, many voters would actually opt for "none of the above" could they do so. All of this suggests that the theory of majority rule is just that, a theory, and that elections really mean very little in terms of majority rule.

But in all fairness to the system, the issues are too many and too complex to be decided by a majority voting for one candidate or another, or one political party or another. The danger lies in assuming that a majority agrees with everything that a successful candidate or political party has espoused. It may be forgotten that both major political parties contain a wide spectrum of views on many issues and many, if not most, thoughtful voters are conservative on some issues and liberal on others. So it turns out that an elected candidate may have little if any real knowledge about the will of the majority on many issues, since the only will that was expressed was that he or she be elected rather than an opponent. The majority was silent on other issues and there are no hard data from the election unless (in those states where it is possible) there happened to be an initative or referendum on a particular issue on the ballot.

If majority rule with respect to the issues is working no better than it appears to be in practice, then what if anything is taking its place? It is suggested that the real influence or power now seems to lie with special interest groups. These have come to cover virtually the whole reach of the social, economic and political spectrum and are even to be found within the bureaucracy of government itself. Elected officials, whether in the legislative or executive branches of government, are beholden to and dependent upon special interest groups for information, expertise and support —whether these be consumer groups, ethnic minorities, trade unions, small or large businesses or industries, professional associations, or nonelected persons or groups in the growing legislative or administrative bureaucracies of government. In this environment the great majority, represented by the average citizen who produces the gross national product and pays taxes to support the government and all its works, generally remains silent and certainly does not decide very much. Only occasionally is there a protest such as the widely publicized Proposition 13 in California, but even this is a far cry from majority rule.

Organized medicine has begun to learn to play this new political game, and with some growing skill and effectiveness. But it has yet to bring the

full strength of medicine, the other health professions and indeed the whole health care enterprise fully to bear. It is true that physicians represent a special interest group on the political scene, but what is not so generally recognized is that their special interest (and that of the larger health care enterprise) is a very broad one. It reaches out to that huge silent majority which seems somehow to have become disenfranchised and replaced by sometimes powerful and sometimes just vociferous special interest groups promoting special causes. Medicine, with its genuine concern with human health and well-being, can touch just about everyone everywhere. And this could be important for the future of this profession.

The medical profession is now being seriously challenged for its leadership in health care, and let there be no doubt about this. The future role of physicians in medical practice will be quite different if some advocates of formidable special interest groups in both the public and private sectors have their way. It is not too soon for the medical profession to get even further into the political game as it is now being played. It is time to begin to mobilize its colleagues in the health professions and in the health care enterprise and to find genuine solutions to the health care problems that concern the public. Particularly, it is time for the profession to begin to identify itself clearly with the special interests of that huge, silent majority, the American public, that is concerned with personal health, well-being and quality of life. The role should be a familiar one for physicians. Quite simply it is the familiar doctor-patient relationship, but in a new and much broader dimension. One might add that, as is so often the case in medical practice, the time is short and the occasion instant.

—MSMW

Iatrodemics and Iatrodemiology

CLEARLY MEDICAL SCIENCE has made major advances possible in patient care during the past 50 years, and the lives of millions of patients have been improved. But there is another side to this coin. In retrospect, some of what was accepted as good scientific medical practice, often over a period of many years, subsequently—with further data and further progress in research—turns out not to have been as beneficial as was thought or even to have been harmful. Sometimes this occurs on a substantial scale, even reaching epidemic proportions. This phenomenon may be described by the term *iatrodemic,* which means iatrogenic disabilities on an epidemic scale.

For example, between 1961 and 1970 many thousands of patients were diagnosed as suffering from pulmonary embolism based on what was thought to be a good clinical history and the use of an advance in technology, the perfusion lung scan. It has become clear that many of the cold spots found on perfusion scanning were nonspecific and did not represent pulmonary embolism. A conservative estimate is that 80 percent of those patients diagnosed as having pulmonary embolism between 1961 and 1970 did not have it.[1-3] This very large number of patients were mistreated in terms of what we know now. Therefore, based on what we do know today, one can say that an epidemic of iatrogenic disease and disability, an iatrodemic, occurred as a result of treating a very large number of patients, often very aggressively, for pulmonary embolism that most did not have. This iatrodemic arose primarily because there never had been and still has not been an adequate randomized prospective trial validating the accuracy of ventilation and perfusion scanning in pulmonary embolism.

For another example, for many years (probably since 1907[4]) radical mastectomy was the treatment of choice for carcinoma of the breast. There is no way to estimate accurately the number of patients treated in this way, but the figure may run into the millions. In 1955 a Scottish physician, McWhirter, published a report of a small series of patients that suggested that simple excision of tumor followed by radiation therapy gave results that were as good as those of radical mastectomy.[5] However, these results and similar results by others were either ignored or discounted. But during the past five years substantial data have accumulated to show that in cases of localized breast tumor, the use of lumpectomy plus radiation produces survival rates not significantly different from those of radical mastectomy.[6] Although the issue has not been entirely settled, many experts now accept the latter approach as at least an acceptable alternative; thousands of women are being spared a physically and emotionally damaging procedure because

radical mastectomy is no longer considered the only acceptable form of therapy. This iatrodemic arose because of an a priori analysis based on an interpretation of the biology of cancer that is no longer considered tenable.[7] No adequate clinical trials were done and, in the final analysis, the practice was based on faith or belief.

These two examples have common characteristics. Each was based on an a priori analysis that seemed sufficiently convincing so that the approach gained general acceptance. There was no real data base for either of the practices. In retrospect, each iatrodemic might have been avoided by relatively small early studies testing the a priori hypothesis.

It should be made clear that this communication does not refer to *iatroendemics*—illnesses and disabilities caused by the inappropriate use of treatment or from an accepted risk of an appropriate use. These iatrogenic happenings will always be endemic and are an inevitable part of patient care, and it is no secret that physicians should and often use these experiences with these untoward events to practice better medicine.

The science of *iatrodemiology* can be an important field in clinical medicine, and most physicians, whether in practice or research, could function as *iatrodemiologists*. The causes of iatrodemics are multiple and complex. Not only are real advances rapidly adopted in practice, but our almost instantaneous system of medical communication also disseminates untested approaches to patient care that may later prove to be incorrect or dangerous. Adequate clinical trials can be extraordinarily difficult to carry out, and it is not easy to detect small benefits or small injuries in small studies based on small numbers. And science itself has its own limitations and difficulties.[8] Then, too, there is an important bandwagon effect when publication of an inadequate study in a reputable journal may lead to general adoption of the published approach. It may be that only one or two reviewers stand between the advocate of a particular practice and those patients who may subsequently receive a new therapy.

It is not traditional for those who introduce errors to take the responsibility for correcting them. The reversal of an error often is an exceedingly slow process. Introduction of a practice (which may later prove to be bad) rides a jet; its elimination from accepted practice is more apt to crawl. Whether we as a profession have taken adequate steps for correcting our errors is an open question. There is no organized forum for dissemination of new information that explicitly refutes previous error. There is no *American Journal of Errors, Retractions and Amendments.* Given the complex causes of iatrodemics, there is no simple answer to preventing them. One step would be to develop organized approaches for critical analysis of current practices and provide an organized forum so that we can systematically learn from our errors and correct them. Should journals like this one provide such a forum? How many iatrodemics can we eliminate and how many can we prevent?

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If Preventable Why Not Prevented?

TWO TIMELY REPORTS on osteoporosis and estrogen therapy appear elsewhere in this issue. Specht points out the relationship between hip fractures and postmenopausal bone loss, and their prevention by administration of low doses of estrogens. Rosenberg and co-workers, in a careful case-control study, confirm previous reports that postmenopausal estrogen replacement, unlike oral contraceptives, does not increase the risk of stroke. Other studies, still in press but soon to be available, further support the findings of these reports and add the information that hip fractures occur far less frequently in estrogen-treated women (11 percent as frequent in castrates receiving long-term estrogen therapy as in untreated comparable controls, according to Paganini-Hill[1])

and that the doses of estrogens needed to prevent postmenopausal or postoophorectomy bone loss are very small. In fact, the work from Judd's laboratory at the University of California, Los Angeles (UCLA)[2] described in abstract form by Specht, shows that the postmenopausal rise in the urinary calcium/creatinine ratio, taken as an estimate of bone breakdown, can be prevented by as little as 0.3 to 0.6 mg of conjugated estrogens or 10 μg of ethynyl estradiol, doses too small to cornify the vaginal mucous membrane and, therefore, to produce endometrial hyperplasia. These doses of estrogens are also smaller than those which have been specifically exonerated from association with any type of tumor, endometrial or other.[1,3]

For those women who cannot take the low doses of estrogens because of medical contraindications such as previous breast cancer, invasive endometrial cancer, fibroids or, most common, migraine, and for those women who will not take estrogens in any form or dosage in these days of excessive anxiety regarding cancer, other osteotrophic agents can be substituted. Fortunately, a whole host of effective agents have been identified recently: progestins,[4,5] anabolic steroids,[6,7] calcitonin[8-10] and, less effective, calcium carbonate[11,12] and calcium gluconate.[12]

We now know that 120,000 to 150,000 white women, most of whom are more than 70 years old, have hip fractures each year in the United States.[13,14] For some unknown reason, black women are largely exempt; however, Asian[15] and Latin-American women, who make up a large portion of the elderly female population in the western part of the country, are not so fortunate. Most women with hip fractures have far-advanced osteoporosis, usually with vertebral compressions, loss of height and varying degrees of invalidism. In addition to the human cost of pain and deformity, *the dollar cost is now at least a billion dollars a year.* Medicare alone paid out $525 million for short-term costs resulting from hip fractures in 1979.[16] This did not include payments from other sources or for long-term care in nursing homes.

As the elderly female population increases, the human and dollar costs will predictably increase unless a program of prophylaxis is introduced. Fortunately, as the Endocrine-Metabolic Advisory Committee of the Food and Drug Administration (FDA) concluded on February 18, 1977,[17] and the Obstetrics-Gynecology Advisory Committee of the FDA concluded on July 28, 1977,[18] "estrogens are effective in preventing postmenopausal bone loss"; the Obstetrics-Gynecology Advisory Committee added, "the risks are acceptable." Unfortunately, the FDA has not yet ruled on these conclusions from its own advisory committees, largely, I suppose, because of the fear that they may be endorsing a carcinogenic agent. But low doses of estrogens, sufficient to prevent postmenopausal bone loss, do not increase the risk of cancer in women. In studies where staging is reported, the forms of endometrial cancer associated with larger doses of estrogens are 95 percent stage I or II.[19] There is no reason to believe that doses of estrogens too small to cause endometrial hyperplasia will produce the histologic changes being read, or misread, as stage I or II cancer. The careful work of Gambrell and colleagues[20] has shown that for women requiring larger doses of estrogens, which can cause endometrial hyperplasia, a 10-day course with a progestational agent each month can reduce the incidence of endometrial cancer to a sixth of that in untreated women. It is not necessary to give estrogens or other osteotrophic agents to prevent osteoporosis in all women. For example, black women and those with severe hypertrophic arthritis do not seem to have bone loss to the degree where fractures occur. To ascertain who is at risk years before fractures occur, readily available measurements of bone mass such as cortical thickness or photon absorptiometry) can show significant bone loss as little as three years after menopause or oophorectomy. Very early bone loss, 6 to 12 months after oophorectomy, can be detected by computerized tomography by any of the 1,500 body scanners in this country.[21]

Not long ago, the United States embarked on a program of prevention for swine influenza at an enormous dollar cost, with the unfortunate production of vaccine-induced Guillain-Barré paralysis and some deaths. The expected epidemic of swine influenza did not occur. In contrast, we can be certain that there will be more than 120,000 cases of osteoporotic hip fractures with more than 15,000 deaths each year. (Endometrial cancer caused 2,397 deaths in 1975, a number that has remained virtually constant for the last 12 years.) Dr. Specht correctly points out the relative threat to life and health of estrogen-associated endometrial cancer versus that of osteoporotic hip fracture. Rosenberg and co-workers allay the fear of cardiovascular risk. The evidence is that most

osteoporotic hip fractures can be prevented and the doses of estrogens necessary to prevent postmenopausal osteoporosis are small and safe. We hear a lot about public health and geriatric medicine, and their ever-increasing costs. One of the few catastrophes of old age that can be prevented is hip fracture. If osteoporotic hip fractures, which constitute the bulk of the problem, can be prevented (and the evidence is that they can be) with a prophylaxis that is cheap and safe, then why not prevent them?

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Magnesium

AMONG CATIONS of biologic importance, magnesium is the forgotten member. It is the predominant divalent cation within cells and, hence, can hardly be classified among the "trace elements," as it oftentimes is. What is implied by this assumption is that our appreciation of the role of magnesium in biologic processes is undeservedly limited.

To place the role of magnesium in biologic processes in proper perspective, it might be helpful to recall that magnesium has played an important role in the evolutionary process ever since the planet earth appeared about 4.6 billion years ago. The predominant mineral of the earth's mantle, as it cooled, was olivine ($[Mg,Fe]_2SiO_4$), which by erosion served as a plentiful source of ionic magnesium to soil and water. Magnesium probably participated in the inorganic condensation reactions which eventually resulted in the appearance of organic compounds from whence arose anaerobic bacteria, the first form of life. (The atmosphere of the earth intially was without oxygen.)

There followed the evolution of chlorophyll, with magnesium as its central atom, and green plants appeared, transforming the atmosphere to contain oxygen, even as solar energy was captured by the chlorophyll for the synthesis of carbohydrate. The ubiquitous adenosine triphosphate (ATP) evolved as the storehouse of chemical bond energy; wherever there is ATP, there is an obligatory need for magnesium in the biologic machinery. As the biochemical mechanisms improved in efficiency and as oxidative phosphorylation evolved, aerobic bacteria and multicellular plants appeared, followed by animals. Protein synthesis requiring the involvement of ribonucleic acid (RNA) and the genetic mechanism involving deoxyribonucleic acid (DNA) both have an obligatory need for magnesium.

From an evolutionary standpoint, therefore, magnesium deficiency can develop in plants when the soil content of this mineral is depleted by weathering and is not corrected by replacement. In animals feeding on plants with magnesium depletion the same deficiency may develop; such a deficiency is recognized in cattle as grass staggers. The clinical syndrome in humans may be conditioned by not only a magnesium-deficient diet, but by other factors such as the availability

of absorbable magnesium in the diet and the additional need for magnesium during stress, as during pregnancy, lactation, or greater growth rate in children.

Elsewhere in this issue, Dr. Flink has expertly reviewed the clinical manifestations of magnesium deficiency in animals and in humans. Clinically, magnesium deficiency is manifest in disease states primarily because of either interruption of food intake or intestinal or renal loss of the mineral. In chronic alcoholic patients magnesium deficiency may develop because of an unbalanced diet and caloric dependence on alcohol. Children with protein-calorie malnutrition (kwashiorkor) may have accompanying magnesium deficiency, which can be corrected by magnesium supplementation, as has been reported in the now classic studies by Caddell.[1] More intriguing is the possibility of marginal dietary magnesium intake and minimal magnesium content in drinking water being correlated with a high incidence of hypertension or coronary artery disease, and the possible relationship of subclinical magnesium deficiency to increased incidence of cardiac arrhythmia. Hard drinking water may be protective.

An empirical but rational load test is now available to detect the presence of magnesium deficiency. It should be used more frequently, because the test is simple to carry out, is almost risk-free (except in the presence of severe renal failure) and is relatively inexpensive.

In the event that magnesium deficiency is suspect, a therapeutic trial of supplemental magnesium may be in order. Again, the risks are minimal.

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CASE REPORTS

Refer to: Zimmerman GA, Crapo RO: Adult respiratory distress syndrome secondary to high altitude pulmonary edema. West J Med 133:335-337, Oct 1980

Adult Respiratory Distress Syndrome Secondary to High Altitude Pulmonary Edema

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ALTITUDE EXPOSURE is associated with a number of adverse effects in humans. Consequences vary from the mild, rapidly reversible syndrome of acute mountain sickness to life-threatening high altitude pulmonary edema (HAPE).[1,2] High altitude pulmonary edema is described as an illness that rapidly responds to rest, administration of oxygen or descent to lower elevation (or combinations of these measures),[2-4] unless immediate death occurs because of severe pulmonary edema and hypoxia. Acute respiratory failure requiring prolonged mechanical ventilation associated with altitude exposure has not been reported. This paper describes two cases in which altitude exposure preceded severe acute respiratory failure and may have contributed to its development.

Reports of Cases

CASE 1. A 26-year-old man drove from his home in Las Vegas, Nevada, (elevation 600 m) to Red River, New Mexico, (elevation 2,600 m). The day after arriving he had a slight headache.

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ABBREVIATIONS USED IN TEXT

C_{th} = static thoracic compliance
HAPE = high altitude pulmonary edema
$P(A\text{-}a)O_2$ = alveolar-arterial oxygen difference
$\overline{PAP}$ = mean pulmonary artery pressure
PEEP = positive end expiratory pressure
PVR = pulmonary vascular resistance
Pw = pulmonary artery wedge pressure
$\dot{Q}_s/\dot{Q}_t$ = intrapulmonic shunt fraction

Over the next three days a more severe headache, progressive dyspnea and malaise developed. During this time he did physical labor at altitudes of 2,700 to 2,900 m. The next day he was somnolent and noted severe dyspnea, cough and scanty white sputum. A physician in Taos, New Mexico, (elevation 2,150 m) found him to have a blood pressure of 130/80 mm of mercury, pulse of 140 per minute, ventilatory rate of 60 per minute and temperature of 38.3°C (101°F), with cyanosis and dry mucous membranes. The lungs had diffuse rales. No abnormal cardiovascular findings were noted other than tachycardia. The hematocrit was 49 percent. His leukocyte count was 32,000 per cu mm, with 72 percent neutrophils, 9 percent lymphocytes, 5 percent monocytes and 2 percent eosinophils. Examination of a sputum specimen showed no cells or organisms. The arterial oxygen pressure (Pa_{O_2}) was 29 mm of mercury, the arterial carbon dioxide pressure (Pa_{CO_2}) was 31 mm of mercury and the pH was 7.47 with the patient breathing oxygen at 8 liters per minute. A radiograph of the chest showed a normal heart size and bilateral alveolar infiltrates. A presumptive diagnosis of nonbacterial pneumonia was made and intubation, mechanical ventilation and treatment with erythromycin was carried out. Hypotension without evidence of shock was treated with fluids, albumin and dopamine. The next day he was transferred by air to the Intermountain Respiratory Intensive Care Unit (IRICU) in Salt Lake City (elevation 1,400 m). His temperature was 38°C (100.4°F), pulse 140 per minute and blood pressure 114/72 mm of

mercury; there were fine rales over both lung fields. A radiograph of the chest showed bilateral alveolar and interstitial infiltrates. Breathing 100 percent oxygen (fraction of inspired oxygen [FIO_2], 1.0), the Pa_{O_2} was 63 mm, the Pa_{CO_2} was 37.5 mm and the alveolar-arterial oxygen difference ($P[A\text{-}a]O_2$) was 505 mm of mercury. The intrapulmonic shunt fraction ($\dot{Q}_s/\dot{Q}_t$) was .51, and the static thoracic compliance (C_{th}) was 21 ml per cm of water. The mean pulmonary artery pressure ($\overline{PAP}$) was 43 mm of mercury, the pulmonary vascular resistance (PVR) was 3.3 mm of mercury per liter per minute and the pulmonary artery wedge pressure (Pw) was 17 mm of mercury. He was treated with mechanical ventilation, positive end expiratory pressure (PEEP), dopamine, gradual diuresis and continued erythromycin. His condition gradually improved and the endotracheal tube was removed on the fifth hospital day. Cultures of sputum, blood and urine were negative (including samples drawn before administration of antimicrobials), as were cold agglutinins, and serologic studies for viruses and Legionnaires' disease. It was necessary for him to remain in hospital for another 12 days because of continued hypoxemia. At the time of discharge the $P(A\text{-}a)O_2$ was 26 mm of mercury, with the patient breathing room air.

Review of his past history showed that five years earlier dyspnea, tachypnea, cough and weakness developed 24 hours after driving from Las Cruces, New Mexico, (elevation 1,200 m), to Red River, New Mexico, (elevation 2,600 m). There had been no exposure to infection, dusts or toxic gases. Physical examination 48 hours after arriving in Red River yielded the following findings: cyanosis, a temperature of 38.9°C (102°F), mild hypotension, tachycardia, tachypnea, diffuse fine rales over both lung fields, and cool, pale extremities. A radiograph of the chest was described as showing "flocculent" infiltrates involving most of the right lung and upper portions of the left lung, with a normal sized heart. Blood gas studies were not available. He was treated with oxygen, intermittent positive pressure breathing (IPPB), and antimicrobials; there was symptomatic and radiographic improvement by the next day, and minimal residual radiographic changes 72 hours after admission.

CASE 2. A 43-year-old man drove from his home in San Diego to southwestern Colorado for a hunting trip. After 48 hours of hunting on foot at elevations to 3,650 m a nonproductive cough, dyspnea, fatigue and vague chest pains developed. The following day he left to return to his home but the cough persisted and his dyspnea became progressively worse. A physician in Richfield, Utah, (elevation 1,600 m), described tachypnea, tachycardia, bilateral rales, "low-grade" fever and bilateral diffuse infiltrates on a radiograph. There was no history of cardiopulmonary disease except for one episode of pneumonia that occurred at sea level. He was treated with oxygen, aminophylline, clindamycin and gentamicin. However, his condition did not improve and intubation and mechanical ventilation were required. On the next day he was transported by air to the Intermountain Respiratory Intensive Care Unit breathing 100 percent oxygen with PEEP of 5 cm of water. On arrival the patient's temperature was 38.5°C (101.3°F), blood pressure 120/60 mm of mercury and heart rate 140 beats per minute. There were diffuse late inspiratory rales noted and the remainder of the examination gave normal findings. An electrocardiogram was normal except for sinus tachycardia. A radiograph of the chest showed patchy alveolar infiltrates with a normal heart size. Arterial blood gas studies (FIO_2 1.0 with 5 cm of water PEEP) showed a Pa_{O_2} of 81 mm mercury, Pa_{CO_2} of 36 mm of mercury, pH of 7.36, $P(A\text{-}a)O_2$ of 483 mm of mercury and $\dot{Q}_s/\dot{Q}_t$ of .25. The C_{th} was 24 ml per cm of water, the $\overline{PAP}$ 34 mm of mercury, the PVR was 2.3 mm of mercury per liter per minute and Pw was 15 mm of mercury. Treatment with diuretics, continued administration of antimicrobials and PEEP resulted in gradual improvement and extubation on the fifth hospital day. It was necessary for the patient to remain in hospital for two weeks because of continued hypoxemia, low-grade fever and mild leukocytosis. Cultures of sputum, blood and urine specimens collected on admission and of multiple specimens drawn subsequently grew no pathogens. Serologic studies for viruses, mycoplasma, Q fever, psittacosis and cold agglutinins, antinuclear antibodies, and lupus erythematosus cells were negative. He returned to full activity after a short convalescence.

Discussion

In case 1 there were a number of features suggestive of HAPE, including age, time course of onset, the history of physical exertion at altitude,

the clinical presentation, the lack of documented infectious (or other) cause and the history of a previous episode.[3] The episode occurring five years earlier conforms to Hultgren's description of the classic clinical presentation and course of HAPE.[5] The major difference between the patient's second episode and the usual clinical course of HAPE was its severity and prolonged nature, requiring intubation and mechanical ventilation for five days and oxygen therapy for another 12 days. The patient in case 2 also had symptoms and a time course of development that were suggestive of HAPE, but his condition did not improve with descent to lower elevation and severe, prolonged respiratory failure developed. In both patients mechanical ventilation, PEEP and other supportive measures were required because of refractory hypoxemia which did not respond to administration of 100 percent oxygen.

Rapid clinical improvement is the general rule in survivors of HAPE.[3,4] However, in spite of treatment with oxygen or descent to a lower altitude, some patients will have physiologic abnormalities that persist for 18 to 24 hours,[6,7] symptoms that last for 24 to 72 hours[3,4,6] and radiographic abnormalities that persist for two weeks.[3] Hypoxemia that does not respond to oxygen administration is not a common feature.[3] The development of severe, prolonged acute respiratory failure in these patients in a setting and with an onset typical for HAPE suggests that altitude exposure may initiate a state similar to the adult respiratory distress syndrome (ARDS)[8] in some persons.

Movement of protein-rich fluid out of the pulmonary capillaries is thought to be a key pathophysiologic event in both HAPE[3] and ARDS,[8] although the protein content of alveolar fluid in patients surviving HAPE has not been measured. The lungs of patients with fatal HAPE are described as having hyaline membranes and alveolar fluid which appears to be rich in protein,[3] similar to the findings in patients dying of ARDS.[8] Experimental work suggests that pulmonary hypertension due to uneven pulmonary vascular obstruction may be associated with increased-permeability edema,[9] an observation that is important in view of the evidence implicating pulmonary hypertension as a key mechanism in the development of HAPE.[3,10] Thus, altitude exposure appears to cause lung edema with increased protein content under some circumstances and may have contributed to the severe acute respiratory failure[8] in the cases we have described. In addition to pulmonary hypertension, some persons exposed to altitude may also be subjected to other influences that may contribute to increased pulmonary capillary permeability. These include cerebral edema[2,11] or hypoxia,[12] associated infection,[3,8] loss of consciousness with gastric aspiration,[8,13] or drugs such as salicylates[11] which may be taken for other symptoms of altitude illness.[1,2] None of these factors were documented in these two cases.

Because most cases of HAPE occur in remote areas, it is possible that those persons with more severe pulmonary edema do not respond to oxygen therapy or descent, and die rapidly. In such cases a prolonged course, similar to that in the cases reported here, might occur if other supportive measures prevented death from the acute illness. A series of cases from Leadville, Colorado,[3] suggests that such a course would be unusual at moderate altitudes. However, as altitude-related disease becomes more frequent[1] it is likely that previously unrecognized manifestations will be encountered. The cases described here suggest that altitude exposure may, under some circumstances, contribute to the development of severe acute respiratory failure. Further experience will be necessary to document the frequency of this complication when respiratory disorders develop in association with ascent to high altitudes, and to identify the mechanisms involved.

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Brill-Zinsser Disease in North America

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THE ILLNESS NOW KNOWN as recrudescent typhus or Brill-Zinsser disease probably has been known to physicians for more than 80 years. In 1898 Brill described the cases of 17 patients with an illness resembling typhoid fever, with the exception that all had a negative Widal reaction. By 1910 Brill[1] had collected and reported on 221 cases of this clinical syndrome, most of which occurred in European immigants. In 1934 Zinsser reported 538 cases of Brill* disease which he had collected over some 30 years; 95 percent of these patients were immigrants from eastern and southeastern Europe who had lived in areas where typhus had occurred in epidemic form. Zinsser[2] suggested that Brill disease represented a recrudescence of epidemic typhus originally acquired in Europe. In 1950 Murray and co-workers[3] reported 14 cases of Brill disease and showed by clinical and serological data that the cause was *Rickettsia prowazeki,* the same agent responsible for epidemic typhus. These authors concluded that the clinical diagnosis could and should be made when a fever of unknown origin occurs in a foreign-born person who lived in an area where typhus occurs in epidemic form; when intense, persistent headache occurs, and when a macular and maculopapular rash develops on the fourth to sixth day of illness. There was final proof of the causative agent in 1954 when Price[4] isolated viable *R prowazeki* from abdominal lymph nodes removed from two patients who had immigrated from Russia 20 years earlier and who apparently had had typhus before coming to the United States. Recrudescent typhus is undoubtedly still with us, but has rarely been reported in the 1970's. Our case appears to be the second report of this disease in North America in more than a decade, the other case having been reported in Canada.[5]

*THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

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Report of a Case

A 54-year-old man, a machinist, was admitted to Mercy San Juan Hospital in Carmichael, California, on July 1, 1974. Symptoms of illness had developed on June 11, which included headaches, sore throat, fever and enlarged cervical lymph nodes. Three days later he was afebrile, but after six days he began to complain of right upper quadrant abdominal pain; a physical examination at that time disclosed no abnormalities. When examined again on June 30, the patient complained of having severe, steady headaches, temperatures to 38.4°C (101°F) daily for the previous six days and right lower quadrant abdominal pain. His medical history disclosed that he had had epidemic typhus infection in a German concentration camp in Poland in 1944.

On examination at admission the patient, who was found to be heavy-set, had a blood pressure of 160/100 mm of mercury, temperature of 39.6°C (103.4°F) and a heart rate of 86 beats per minute. There were two enlarged nontender cervical lymph nodes, both less than 5 mm in diameter. The neck was supple, the abdomen was soft and nontender, and the skin was hot and dry. There was no rash at the time of admission. There was no hepatomegaly or splenomegaly.

Serial blood counts disclosed a continuously normal leukocyte count with a slight left shift and some toxic granulation of the neutrophils. Results of analysis of urine and urine culture were normal. Six blood cultures failed to yield growth. Lactic dehydrogenase (LDH) determinations were slightly elevated with no specific pattern on isoenzyme testing. On admission serum aspartate aminotransferase (formerly serum glutamic oxaloacetic transaminase [SGOT]) levels were normal at 26 with subsequent rise to 60 units (normal 0 to 50 units). Skin tests for coccidioidomycosis, histoplasmosis, tuberculosis and mumps all yielded negative results. No bacterial pathogens were isolated from specimens from the throat or the feces. Results of examination of cerebrospinal fluid were normal. A screening test for infectious mononucleosis was negative. The titer for antistreptolysin was less than 166 Todd units. Findings on roentgenograms of the abdomen, skull and chest, intra-

venous pyelogram, upper gastrointestinal series, small bowel series and a barium enema study were all normal. Nucleide brain scan and an electrocardiogram showed no abnormalities.

The patient's clinical course was notable for the presence of a continuously severe headache, temperatures ranging between 37.8°C (100°F) and 39.5°C (103°F), myalgia and weakness. On the sixth hospital day, a macular rash appeared transiently on the abdomen, back and arms, returning the following day in a general distribution, but was not visible thereafter. After diagnostic studies were completed, a regimen of 250 mg of tetracycline given orally four times a day was initiated on the eighth hospital day, with defervescence within 48 hours. Headache ceased 24 hours after institution of antibiotic therapy. Strength and the ability to walk returned and the patient was discharged on the tenth hospital day.

Discussion

This patient's symptoms and signs—high fever, intense and unrelenting headache, a transient macular rash on the trunk during the height of the illness and prompt response to tetracycline therapy—are all typical of Brill-Zinsser disease. On the other hand, the patient's history of an illness characterized by pharyngitis and intermittent low-grade fever for approximately three weeks before the development of the classic features of recrudescent typhus are not characteristic of that disease, as the latter generally has a short, three- to four-day prodromal period.[3] It is doubtful, then, that the patient's earlier symptoms were those of recrudescent typhus but more likely were representative of some nonrickettsial process. The diagnosis in this case was substantiated by the antibody test results (Tables 1 and 2). Complement fixation titers to the typhus group antigen were elevated significantly in the late acute phase of the patient's illness as well as five weeks later, with an eightfold fall occurring several months later, indicating either epidemic typhus or murine typhus. The first two serological studies showed significant elevations to *both* the specific epidemic typhus and the related murine typhus antigens. Indirect fluorescent (IFA) titers on the three serum samples showed somewhat higher titers to the epidemic typhus than to the murine typhus antigen (Table 1). IFA tests carried out on the first serum sample after differential absorption with yolk sac, as a control, as well as the nonpathogenic *Rickettsia canada* and epidemic typhus and murine typhus antigens (Table 2) confirmed that the antibody was specific for epidemic typhus. It was completely absorbed with epidemic typhus antigen but not with the murine typhus antigen or *Rickettsia canada*. Furthermore, the antibody was found to be almost all IgG, the characteristic response in Brill-Zinsser disease, in contrast to primary epidemic typhus and murine typhus in which IgM antibody predominates early in the disease.

TABLE 1.—*Results of Initial Serological Tests*

Antigen	*Technique*	*Dates of Serum Samples* 7/9/74	8/14/74	2/28/74
Rocky Mountain spoted fever	CF*	1:8	1:8	ND
Typhus group	CF*	1:512	1:512	1:64
Epidemic typhus	CF†	1:512	1:512	ND
Murine typhus	CF†	1:256	1:256	ND
Epidemic typhus	IFA†	1:8,192	1:2,048	1:512
Murine typhus	IFA†	1:2,048	1:256	1:128

CF = complement fixation; IFA = indirect fluorescent antibody; ND = not done

*Done at the Viral and Rickettsial Disease Laboratory of the State of California Department of Health.
†Done at the Leprosy and Rickettsia Branch of the Virology Division of the Bureau of Laboratories, Center for Disease Control, Atlanta.

TABLE 2.—*Results of Special Indirect Fluorescent Antibody Tests on Serum Sample of 7/9/74**

Antigen	Absorption With: Yolk Sac	Murine Typhus	Epidemic Typhus	*Rickettsia canada*
Murine typhus	1:1,024	1:64	1:16	1:1,024
Epidemic typhus	1:16,384	1:4,096	1:16	1:8,192
Rickettsia canada	1:1,024	1:16	1:16	1:16

*Done at the Leprosy and Rickettsia Branch of the Virology Division of the Bureau of Laboratories, Center for Disease Control, Atlanta.

This case illustrates that Brill-Zinsser disease can appear some 30 years after the initial bout of louse-borne typhus, due to the fascinating ability of the responsible microorganism, *R prowazeki,* to remain dormant in the reticuloendothelial system for many years. The reasons for recrudescence have never been elucidated.

In contrast to cases of classic louse-borne typhus, recrudescent typhus carries a low mortality, and the untreated disease is shorter in duration than classic typhus. Nevertheless, it is clear that patients with Brill-Zinsser disease, such as our patient, can remain in a toxic condition and be ill for many days; also, fatalities have been described.[1,3] The severe, unrelenting headache generally persists throughout the 10- to 14-day

febrile course and its response to symptomatic therapy is usually poor. The rash typically begins on the fourth to sixth day of the illness and consists of small, discrete macules of 1 to 10 mm which are generally noted first on the chest or abdomen, but which can be present later on the extremities. The rash may be transient, as in our patient, or persist for a few days. The response to the tetracycline group of antibiotic drugs is excellent, as in epidemic typhus, and it has been noted recently that even one dose of doxycycline can lead to prompt defervescence.[6] Therefore, therapy with a tetracycline drug should be initiated when classic features are present.

In contrast to epidemic typhus, Brill-Zinsser disease is not generally associated with a positive Weil-Felix test; for example, in our patient, the *Proteus* OX19 titer was only 1:20. The complement fixation test generally attains a maximum level by the 10th to 11th day of illness in contrast to epidemic typhus in which the maximum titers are not usually achieved until two weeks after onset. Therefore, in suspected cases it is important to obtain serum samples during the acute phase of illness for antibody testing to demonstrate a later rise in titer.

It was postulated by Murray and co-workers in 1950 that large numbers of cases of Brill-Zinsser disease might be found in this country due to the large influx of immigrants who had experienced typhus in Nazi concentration camps and elsewhere during World War II.[3] However, very few cases have been reported in North America in the 1960's and 1970's; the last case was reported in Canada in 1974.[5] Possibly, the rarity of recent reports of this disease is due partially to unfamiliarity with its manifestations and the lack, therefore, of attempts to make a specific diagnosis. We hope that this case report will stimulate continued attempts to diagnose Brill-Zinsser disease in the future.

Summary

A case of recrudescent typhus occurring 30 years after the initial bout of epidemic typhus is described. This disease should continue to be considered in the differential diagnosis of fever of undetermined origin in immigrants, particularly those from eastern Europe, from regions where typhus infection may have occurred in the past. The clinical diagnosis should be confirmed by appropriate serological tests.

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Refer to: Hart MJ, White TT: Choledochocele associated with acute hemorrhagic pancreatitis. West J Med 133:340-344, Oct 1980

Choledochocele Associated With Acute Hemorrhagic Pancreatitis

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CHOLEDOCHAL CYSTS have been reported more than 1,000 times in the medical literature since the first one was described by Douglas in 1852.[1-4] However, the incidence of choledochoceles or type III choledochal cysts as classified by Alonso-Lej[5] is rare, and only 21 cases have been reported.[3,4,6-21] A patient with this type of lesion, which was associated with hemorrhagic pancreatitis and necrosis of the head of the pancreas, was recently treated by us and that case is the basis for this report.

Report of a Case

A 40-year-old man was admitted to Providence Hospital in Anchorage, Alaska, on June 7, 1978, after the sudden occurrence of severe epigastric pain and a temperature that rose to 39°C (102.2°F). The level of serum amylase was 2,700 units (normal less than 200). Past medical history included multiple episodes of abdominal pain.

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Submitted November 5, 1979.

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Previous upper gastrointestinal series had detected a mass in the second portion of the duodenum, which had been noted to appear and disappear since 1966. The patient's abdominal pain, fever and hyperamylasemia resolved over the next two weeks after nasogastric suction and administration of fluids intravenously. A transfusion of two units of whole blood was also required because the hematocrit had dropped to 30 percent. An attempt to feed the patient at this time, however, resulted in a return of abdominal pain and elevation of serum amylase. Central venous hyperalimentation was begun June 21. A cholangiogram after intravenous injection of contrast medium showed that the common bile duct was of normal caliber. An x-ray study of the upper gastrointestinal tract and a computerized tomographic (CT) scan of the abdomen showed a mass in the medial aspect of the second portion of the duodenum. On gastroduodenoscopy a mass was noted protruding from the medial aspect of the second portion of the duodenum. Biopsy studies of this lesion showed only duodenal mucosa.

The patient was transferred to Swedish Hospital Medical Center in Seattle on July 6. On admission he was noted to have epigastric pain, requiring administration of narcotic analgesic drugs. Serum amylase values were normal as was the remainder of the hemogram and chemistry profile. Endoscopy was carried out on the following day, and a soft, smooth, 2- by 3-cm mass was found on the medial aspect of the second portion of the duodenum. The ampulla of Vater was observed at the upper aspect of this structure and was cannulated. Injection with contrast medium showed a fluid-filled cyst without communication with the bile or pancreatic duct (Figure 1).

On July 11 the patient was operated on. Operative cholecystocholangiography showed a normal common bile duct communicating with a choledochocele and with the duodenum at the ampulla of Vater (Figure 2). Exploration of the lesser sac showed pronounced inflammatory response and necrosis of the entire head of the pancreas to the level of the portal vein. The tail of the pancreas appeared to be intact although it was somewhat indurated. There was some necrosis along the superior surface of the pancreas above the splenic artery. Pancreaticoduodenectomy was carried out to restore pancreatic continuity with the gastrointestinal tract and to remove the choledochocele. Continuity with the gastrointestinal tract was restored by end-to-end pancreaticojejunostomy, end-to-side choledochojejunostomy and end-to-side gastrojejunostomy. A Silastic tube was used to stint the pancreatic duct in the postoperative period. It drained copious amounts of clear pancre-

Figure 1.—Choledochal cyst after endoscopic injection with contrast medium. The air-filled shadow of the duodenum can be seen in the background.

Figure 2.—Operative cholecystocholangiogram illustrating the connection of the common bile duct with the elongated choledochocele in the duodenum.

Figure 3.—Photograph of the operative specimen of the duodenum showing the point at which the bile and pancreatic juice entered the duodenum and the adjacent intraduodenal choledochocele.

atic juice, indicating that the remainder of the pancreas was functional. There was an unremarkable postoperative course and the patient was discharged on the 14th postoperative day without evidence of exocrine or endocrine-pancreatic insufficiency. Gross and histological examination of the operative specimen showed that the cyst was 2 by 4 cm in diameter (Figure 3), lined with duodenal mucosa and communicating with the bile duct at the ampulla. The pancreatic duct could not be located. Examination of the pancreas showed necrotic tissue, inflammatory exudate and fat necrosis.

Discussion

Choledochoceles have been described in previous reports as enterogenous cysts of the duodenum[10,15-17] or of the ampulla of Vater,[7,9] and duplication cysts of the duodenum.[14,22] It seems appropriate, however, on the basis of common anatomical and clinical characteristics to refer to these lesions as choledochoceles, as was originally suggested by Wheeler[23] and confirmed by Alonso-Lej and co-workers.[5] A review of the literature uncovered 21 previous case reports that corresponded to this description of a dilatation of the distal bile duct presenting as a mass within the duodenum. Pertinent features of these cases and our case are presented in Table 1.

Incomplete clinical data are available for these earlier cases. Thirteen of the patients were female, eight were male. Their average age was 34 years, with a range from 14 to 73. Of 20 patients in whom symptoms were noted, 18 had abdominal pain, most with an acute episode in addition to a history of intermittent abdominal distress. Pancreatitis was present in 6 of the 20 patients in whom symptoms were reported. A pseudocyst developed in one.[21] In our patient acute hemorrhagic pancreatitis with necrosis of the head of the pancreas developed. Three patients were jaundiced, four presented with anorexia and vomiting and two presented with gastrointestinal bleeding.

The lesion was always identified in the patients in whom upper gastrointestinal series were carried out. It was usually described as a round, filling defect in the second portion of the duodenum. Intravenous cholangiography correctly identified the lesion in four of the nine patients in whom the study was undertaken. In four others, results of the study were interpreted as normal, and in one a dilated duct was seen. The choledochocele was appropriately identified by duodenoscopy or endoscopic retrograde cannulation of the papilla in the four patients in whom it was done. Our patient is the only one in whom the lesion was visualized on a CT scan.

Two anatomical variations of this lesion were observed.[19] The bile duct and pancreatic duct were found to drain directly into the choledochocele in nine cases. The choledochocele then drained through its own orifice into the duodenum. In the nine other cases for which anatomical descriptions are available, the choledochocele presented as a cystic outpouching, draining into the distal bile ducts immediately proximal to the ampulla. Four of the choledochoceles contained gallstones.

Twelve of the choledochoceles were lined with duodenal mucosa, with a layer of muscularis separating the lining from the mucosa of the duodenum itself. In four other patients, the lining consisted of mucosa consistent with the distal bile

duct. In one patient a histological examination showed variable intestinal and bile duct components.

In most cases, surgical therapy consisted of excision of one wall of the choledochocele, essentially marsupializing the cyst into the duodenum, with careful preservation of the bile duct and pancreatic duct sphincters. Sphincteroplasty was used if impingement of the pathological process on these sphincters was suspected. This type of operation achieved excellent results in all of the reported cases. Pancreaticoduodenectomy was used in our patient to remove necrotic pancreatic tissue and restore pancreaticoenteric continuity.

TABLE 1.—*Review of 22 Reported Cases of Choledochocele*

Author/ Date of Report	*Age (yr)/ Sex*	*Symptoms*	*Diagnostic Test*	*Operative Findings*	*Histological Findings*
1. Wheeler[23]/1940	64/M	Abdominal pain, jaundice	..	2×3 cm cyst	None
2. Brooks[7]/1943	30/M	Abdominal pain	UGI	8×15 cm cyst with common bile duct and pancreatic duct entering cyst	Duodenal mucosa
3. Gordimer[10]/1950	30/F	Abdominal pain	..	4×8 cm cyst entering distal bile duct, gallstones in cyst	Duodenal mucosa
4. Polson[17]/1953	20/F	Abdominal pain, vomiting	UGI	3×5 cm cyst with bile duct entering cyst, gallstones in cyst	Duodenal mucosa
5. Alden[6]/1957	18/F	Abdominal pain	UGI	8×15 cm cyst with bile and pancreatic ducts entering cyst	Biliary mucosa
6. Serfas[20]/1957	43/F	Abdominal pain, jaundice	UGI, IVC	3×5 cm cyst entering distal bile duct, gallstones present	Intestinal and biliary mucosa
7. Stephens[21]/1966	18/M	Abdominal pain, pancreatitis	UGI	4×4 cm cyst with bile duct entering cyst	Biliary mucosa
8. Kaftori[13]/1966	18/M	Abdominal pain, vomiting	UGI, IVC	3×4 cm cyst with bile duct entering cyst	Duodenal mucosa
9. Leffall[14]/1967	52/F	Asymptomatic	UGI	8×11 cm cyst entering distal bile duct	Duodenal mucosa
10. Perrin[16]/1969	14/F	Abdominal pain, pancreatitis	UGI, IVC	4×4 cm cyst with bile duct entering cyst	Duodenal mucosa
11. De Oya[9]/1969	19/F	Abdominal pain, pancreatitis	UGI	3×4 cm cyst entering distal bile duct	Biliary mucosa
12. Jansen[12]/1970	15/F	Abdominal pain jaundice, pancreatitis	UGI	3×4 cm cyst entering distal bile duct, gallstones in cyst	Duodenal mucosa
13. Warren[22]/1971	22/M	Abdominal pain	UGI	5×8 cm cyst with bile duct entering cyst	Duodenal mucosa
14. Brunton[8]/1972	33/M	Abdominal pain, vomiting, gastrointestinal bleeding	UGI	Cyst with bile duct entering cyst	Duodenal mucosa
15. Ortiz[15]/1974	14/F	Abdominal pain, pancreatitis	UGI	12-cm cyst entering distal bile duct, gallstones in cyst	Duodenal mucosa
16. Reinus[18]/1976	21/F	Abdominal pain	UGI, duodenoscopy	Cyst entering into distal bile duct	Duodenal mucosa
17. Scholz[19]/1976	59/F	Abdominal pain	UGI	3×6 cm cyst entering distal bile duct	Duodenal mucosa
18. Scholz[19]/1976	73/F	Abdominal pain	UGI, IVC	Choledochojejunostomy, duodenum not opened	None
19. Hadad[11]/1976	50/M	Anemia, gastrointestinal bleeding	UGI, duodenoscopy	Cyst with bile duct entering cyst	Not reported
20. Kimura[3]/1977	..	..	..	..	..
21. Matsumoto[4]/1977	57/F	..	..	..	..
22. Present report/1980	40/M	Abdominal pain, pancreatitis	UGI, CT scan, ERCP	2×3 cm cyst entering distal bile duct	Duodenal mucosa

CT = computerized tomography; ERCP = endoscopic retrograde cholangiopancreatography; IVC = intravenous cholangiography; UGI = upper gastrointestinal (series)

The postoperative convalescence has been without complications (15 months).

The cause of choledochal cysts, particularly that of choledochoceles, remains unclear. The normal development of the gut and bile duct from a solid cord to vacuoles to a tubular structure coupled with epithelial proliferation is a setting in which inequalities of growth might lead to congenital cyst formation.[24] Babbitt suggests that reflux of pancreatic juice into the bile duct causes intermittent low-grade cholangitis with inflammation, dilatation and, finally, cyst formation.[25] Sterling's anatomical studies[26] support an acquired cause. He found evidence of diverticula in the distal common bile duct in 4 of the 70 postmortem examinations. He did not report on the histological anatomy of these cases. His cases were associated, however, with calculi in the common bile duct. For this reason he postulated that impaction of a stone in the papilla could cause increased intraluminal pressure, resulting in a choledochal diverticulum. This theory does not, however, account for the duodenal mucosa that has been found in most choledochoceles.

The fact that 30 percent of the patients reported in the literature had pancreatitis is of particular interest. The presumed cause is obstruction of the pancreatic duct by the choledochocele, which in turn results in acute pancreatitis. Gallstones were found within the choledochocele and may have played a causative role in the pancreatitis in two of the six patients with this disorder. The presence of a choledochocele has not been considered as a cause for pancreatitis in the past. In these cases, however, pancreatitis and choledochocele frequently occurred together. Therefore, a choledochocele should be considered in the diagnosis of young patients with acute pancreatitis but without a history of gallstones, alcoholism or abdominal trauma.

Summary

Our patient represents the 22nd reported case of choledochoceles. The cause of this rare lesion remains obscure. Choledochoceles should be kept in mind as a possible cause of pancreatitis in young patients without a history of gallstones, alcohol abuse or abdominal trauma. Technically, surgical correction is easy and is highly successful in early uncomplicated cases.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Computerized Tomography in the Management of Cerebral Tuberculomas

To the Editor: Computerized tomography (CT) has become a valuable tool in the evaluation of patients with a wide variety of intracranial diseases.[1] We are currently treating a woman with multiple cerebral tuberculomas for whom the CT scan has provided information crucial to her diagnosis and management.

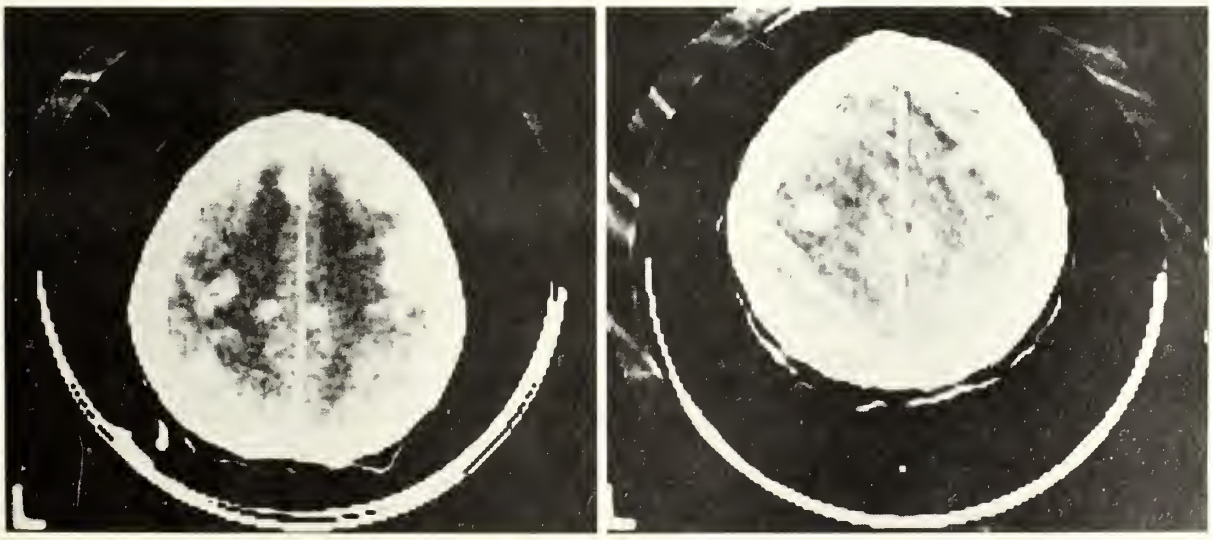
Report of a Case

A 72-year-old Paiute woman was admitted March 3, 1978, because of cough, malaise, lethargy and findings on an x-ray study of the chest that were consistent with miliary tuberculosis. A physical examination disclosed bilateral rales and evidence of a previous cardiovascular accident, with mild left-sided weakness and a left Babinski reflex. Findings of a lumbar puncture included normal pressure, two lymphocytes, and protein value of 73 mg per dl; cerebrospinal fluid and serum glucose values were 53 and 102 mg per dl, respectively. Sputum and urine cultures subsequently grew *Mycobacterium tuberculosis.*

The patient was started on a regimen of isoniazid (INH), rifampin and ethambutol, but pruritis and scleral icterus developed after 12 days, with a serum aspartate aminotransferase (serum glutamic oxaloacetic transaminase) value of 167 units per ml (normal less than 35) and a bilirubin value of 2.6. The patient's symptoms and laboratory abnormalities resolved after isoniazid therapy was discontinued.

She continued receiving rifampin and ethambutol, except during a one-week lapse during a drinking binge. She was doing well until May 16, when her family returned her to hospital, complaining that she had reverted to her native Paiute language and would no longer speak or respond to Navajo, her second language, which was used exclusively at home.

Findings on physical examination were un-



Figures 1 and 2.—Computerized tomograms showing multiple diffuse contrast-enhanced lesions in both hemispheres consistent with multiple cerebral tuberculomas **(left)** and pronounced improvement with the disappearance of all but two small convexity lesions six months after resumption of isoniazid therapy **(right).**

changed, aside from lethargy and confusion. Examination of a fluid specimen from a lumbar puncture gave these values: one polymorphonuclear leukocyte, one lymphocyte, protein of 50 mg per dl and glucose of 37 mg per dl (serum glucose 94 mg per dl).

A CT scan on May 23, 1978, showed multiple diffuse contrast-enhanced lesions in both hemispheres consistent with multiple cerebral tuberculomas (Figure 1). Pyrazinamide and capreomycin were added to the patient's regimen of rifampin and ethambutol; seizures occurred, but were controlled with phenytoin and steroids. She gradually became more oriented and lucid and regained her ability to speak Navajo.

A repeat CT scan in July 1978, again showed multiple lesions in both hemispheres, as did a third scan in October 1978.

Because the cerebral lesions had not resolved despite clinical improvement, capreomycin therapy was stopped after six months and INH was cautiously reintroduced, without recurrence of pruritis or liver abnormalities. A CT scan in June 1979, six months after INH therapy was resumed, showed pronounced improvement with the disappearance of all but two small convexity lesions (Figure 2).

After two years of therapy, all drugs were stopped. She remains free of seizures and is clinically well, and is able to do gardening and weaving of traditional baskets. She has resumed speaking fluent Paiute and Navajo.

Conclusion

Cerebral tuberculoma is a rare complication of disseminated tuberculosis in the United States, although its incidence in other countries may be much higher.[2,3] CT scanning is a valuable tool in showing the location and size of cerebral tuberculomas and is superior to scintigraphy or angiography for this purpose.[4,5] In our patient, it allowed us to follow her response to therapy in a reproducible, noninvasive manner. CT stimulated us to reinstitute INH therapy, despite evidence of previous significant toxicity, because of evidence of an inadequate response to alternative drugs that were possibly less efficacious in treating tuberculosis of the central nervous system.

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Expert Testimony in Court

TO THE EDITOR: The Specialty Conference in the August issue reviewed some elements of controversy in the provision of expert witness testimony in medical malpractice problems. The following is offered to show some areas of promise and hope in this area.

Some medical malpractice suits are filed by a disgruntled patient, or his heirs, because of an unexpected bad result of medical or surgical care. Many such suits have no merit and usually relate to (1) unrealistic patient expectations, (2) poor relation with the physician or hospital staff or (3) a bill deemed by the patient to be excessive. Other suits are filed because of a bad result due to carelessness or the physician going beyond the limits of his training, expertise and experience. Who can then best differentiate between these issues of fact to help to balance this controversy and to equalize the scales of justice between the merely unhappy or the truly medically injured patient and the physician-hospital? The properly qualified medical expert, that is who.

But, let us put one myth alluded to by the editor (in the related editorial " 'Hired Guns' in Court") behind us; the myth of the expert responsible only to the court, the amicus curiae. Our legal system has yet to evolve to this utopian state; the adversary trial system being the present state of the art placing expert against expert on each side of the issue. The ostensible goal of this contest being a search for the truth. Though we must continually strive for a better future system, we must perfect the present imperfect mechanism of justice and realize that only physicians, as unbiased experts, can present fact and opinion evidence which can lead to a fair and just hearing for either the physician-hospital defendant or the injured-deceased plaintiff.

Unhappily, the average physician prefers not

to become involved, and it is not easy for the lawyer to get a local physician to render an opinion for the patient-plaintiff, a reluctance that still makes lawyers wonder about coercion, cowardice or conspiracy.

Who can best evaluate the merits of a potential suit but a seasoned physician well conversant with the specialized issues at bar. His thoughtful, honest and learned review will halt any advancement of the controversy without merit. At least as important, the valid action in negligence can be pursued with full justification and vindication as the fact and opinion evidence is supplied by the medical expert. These efforts and activities should help both physicians and their insurers by (1) removing many suits from the stream of litigation and (2) calling for early pretrial settlements with major savings to insurers and ultimately to the insured in meritorious actions.

The only problem, then, is to secure such expert volunteers who are well qualified both by training and experience. The most effective expert is one who is in active practice and who can then question the activities of a similar practitioner and determine the adherence to the standards peculiar to that field of practice. He can best "stand in the shoes" of the potential physician-defendant and determine the appropriateness of the conduct in question. Finally, the experts or organizations providing expert testimony should seek and receive the approval of their local medical society; such approval can be made known to the court. This should serve to validate such persons and services so as to differentiate between the forces of truth and the "hired guns," and such would serve to qualify experts as quasi-friends of the court.

EARL J. KOLB, MD
Pacific Grove, California

* * * *

To the Editor: There have been many concepts applied towards developing a remedy for abuses of the medical malpractice situation. The concept stated in the August editorial " 'Hired Guns' in Court" clearly heads the list. If expert testimony were mandated to address only "full disclosure" a major step will have been taken. There is precedent in this concept supplied by the recent California Supreme Court decision making physicians liable for errors of omission in this regard.

Progress in the field of law is admittedly decades behind that in medicine. Perhaps it is true that "one of the most advanced types of human being on earth today is the good American doctor" (Alfred North Whitehead). In any event, I feel medical associations should pursue the doctrine discussed in the editorial, and the editorial deserves to be commended.

MICHAEL H. SUKOFF, MD
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Holistic Medicine for Neurosurgeons

To the Editor: This is to thank Dr. Simon Auster of Martinez, California, for taking time to read my brief communication in the March issue on holistic medicine for neurosurgeons and make the reply which appeared in June.

I can assure Dr. Auster that every patient seen by me with a life-threatening situation is given a thorough explanation of the natural course of the disease, of the several procedures available, and of the mortality and morbidity statistically known to complicate each one of these procedures. Only then is the patient presented with his several choices. I might add that it is also a firm policy of mine to explain to every patient who is faced with an operative procedure that if there is any doubt in his mind as to whether or not he wishes to have the procedure done he should not subject himself to the procedure.

Another problem arises when one is faced with an acute emergency, life-and-death situation such as the presence of an acute (traumatic or nontraumatic) intracerebral hematoma. One does not have time in most cases for getting a second opinion or having more than a brief discussion with the family physician. In those cases, going with the nonoperative procedure has in my experience resulted in a fairly large number of deaths.

It is regrettable, indeed, that the scientific and technological advances in many of the specialties and subspecialties can be negated by a system that begets illogical thinking.

On the particular subject of chronic subdural hematomas in the elderly, I have in the past compiled a list of patients over 60 undergoing removal of chronic subdural hematomas with no deaths and minimal morbidity.[1,2] I believe that reproducing these figures under the influence of the "holistic" type of thinking would not be possible.

Another point I would like to raise is that when

Letters to the Editor should be typed double-spaced (including references) with conventional margins. The text should not exceed 600 words.

a surgical procedure is suggested—anything from cataract removal to a knee cartilage operation—a specialist of the appropriate discipline should be called for a second opinion rather than a member of the holistic community. I think that this will not only lead to better patient relationships but also will improve surgical results.

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Dehumanizing Jargon

To the Editor: While deploring the degradation of the English language in the medical realm, the Special Communication "Babel in Medicine?" by Leon Morgenstern and its companion editorial "Will It Be Babble, Babel or Clarity of Language?" (both in the August issue) fail to discuss fully a far more critical reflection of the jargon so accurately portrayed in "Rounds with the Chief."

Dr. Morgenstern briefly alludes to what I feel is the key issue: the "degradation of the . . . beleaguered patient." Referring to a person as "an organ, a disease, an operation, a bed or a room" can only be verbal expression of a coldly dehumanizing attitude which does not consider the whole person. Neglected are the patient's thought processes, belief systems, emotions, and social and family relations which influence and are influenced by the course of his or her illness.

Even more disturbing is how pervasively this jargon and concomitant perspective are incorporated into the professional modus operandi developed by medical students and residents. It is difficult not to be affected by powerful socializing and indoctrinating forces inherent in our training. Conforming to exemplified behavior and attitude has the obvious advantages of pleasing one's superiors (thus gaining favorable evaluations and recommendations) and facilitating adaptation to the intense and stressful environment of a teaching hospital. It is far easier to fit into the mold than to conscientiously develop a philosophy and style of patient care, based on one's inherent idealism, by openly confronting the myriad challenges our work entails and experiencing the fulfillment, frustration, pain or anger they evoke. But most important, developing professionalism is tempered by examples, good or bad, of other people working in the medical system. On several occasions I have heard medical students, housestaff or even attending physicians refer to the "auto versus auto" or "the prostate," but cannot recall more than a rare instance of anyone present speaking out to suggest a more humanistic approach. If indeed "teachers as well as students are the keepers of the flame," then consideration, compassion and respect for patients must be ranked as more important than having complete data for the Chief on rounds, citing journal references with alacrity or producing obscure differential diagnoses.

As repeatedly pointed out in this journal's forum "Orthodox Medicine, Humanistic Medicine and Holistic Health Care," have not the "concepts of humanity, love, kindness and sensitivity"[1] since Hippocrates been basic tenets of an "orthodox" system that has "always encompassed the whole person"?[2] Besides, by maintaining an approach that considers foremost the human beings, not the pathologic conditions, perhaps one can at the same time save the "clarity, accuracy and grammatical purity" of the English language.

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Medicine in the Work Place

To the Editor: Bravo! Dr. Garry S. Brody's brief article, "Holistic Medicine and Unscientific Cults" (West J Med 133:172-173, Aug 1980), is excellent.

Several years ago I was doing a dressing change on the tiny hand of a very young patient and noticed 100 percent takes of small full thickness skin grafts used to correct postburn contractures of three fingers. A nurse's aide standing by exclaimed "Isn't it marvelous what they can do these days."

What *they* can do? Hell, I did it. Institutions, committees, boards, organizations don't *do* things. Individual human beings *do* things.

Talk is cheap and there is sure a lot of it these days. If one's son has an osteogenic sarcoma of the leg, one wants to find someone who can *do* something about it—not someone who can *talk* about

promoting health so that treatment of disease won't be necessary.

As I look about the hospitals, look at governmental agencies and look at the entrenched bureaucracies I get the feeling that soon there will be regulators with no one left to *do* things.

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Relative Value of CPR

To the Editor: The article "Cardiopulmonary Resuscitation in a University Hospital, an Analysis of Survival and Cost," in the October 1979 issue, appears to state that cardiopulmonary resuscitation is effective and cheap when it is neither. Of course, cardiopulmonary resuscitation saves some lives which would otherwise be lost. On the other hand, cardiopulmonary resuscitation does a great deal of harm to an even larger number of patients. This was especially true for the 43 initial survivors who died while still in the hospital. They suffered a lingering death while their families anguished for them. When the benefit and harm are compared, cardiopulmonary resuscitation is not a very effective intervention.

The cost of cardiopulmonary resuscitation should not be minimized. All 67 initial survivors were treated in an intensive care unit, many for prolonged periods. I estimate that their care cost was over $500,000; thus the cost resulting from the intervention is not modest.

The relative value of cardiopulmonary resuscitation is difficult to assess. Articles that mislead readers and oversimplify the problem make it even more difficult to delimit cardiopulmonary resuscitation's appropriate application.

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More on Medicaid in California

To the Editor: It is unusual for a medical journal to accept for publication a report in which conclusions are made that are directly contradicted by the data presented (Myers BA, Leighton R: Medicaid and the mainstream: Reassessment in the context of the taxpayer revolt. West J Med 132:550-561, Jun 1980). Perhaps a special dispensation was given to the chief executive of California's State Department of Health Services in publishing her article on Medicaid and the mainstream.

Ms. Myers claims that Medicaid's costs have risen at an alarming rate, at such a rate that some other method of providing care must be found. Her data presented show that the opposite is true.

Conclusions based on her data would more accurately be as follows: the percentage of California's population eligible for state payment of medical care has more than doubled from 1966 to the present (up 200 percent), the percentage of tax dollars spent on medical care has risen at a much slower rate (up 136 percent), the dollar cost per eligible person has risen much slower (up 172 percent) than the rate of general inflation (over 200 percent), and the state of California has progressively penalized any physician who provides medical care for California residents whose care is paid for by governmental medical care programs.

Does Ms. Myers expect to influence the opinion of physicians or any perceptive reader by using such data as a basis for her unfounded and inaccurate conclusions? Such conclusions have only rhetorical and political value, and they should not be accepted as valid.

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Evaluation of Performance and Outcome

To the Editor: Two articles in the July 1980 issue deserve comment: one is by Paul J. Sanazaro[1] and the other is by Katon and Kleinman.[2] Both articles are concerned with the important question of evaluation of ourselves as doctors. They differ in that Sanazaro is using the scientific or objective approach primarily and Katon and Kleinman are employing the humanistic or subjective approach.

The appearance of the two articles in the same issue should be noticed and applauded. I would call the paper by Sanazaro, by way of metaphor, a triangle. It is constructed of straight lines; it has edges and points, and it is hard in its type of data. I would call the Katon and Kleinman article a circle: round and soft.

Are they incompatible? In a reality that is three-dimensional, they are both parts of a cone: sideways triangular, and circular from below.

Also in the July issue was an article that metaphorically demonstrates the incredibly beneficial effects of the integration of hard and soft attitudes, or, if you wish, cone-ness. I refer to A. Gerber's article "Improved Quality of Life Following a Kock Continent Iliostomy."[3] The originator and

subsequent champions of the Kock procedure went beyond "outcome" in scientific terms and used their concern for quality of life to invent a creative surgical innovation. Is this not germane to the topics discussed in the recent forum in this journal on Orthodox Medicine, Humanistic Medicine and Holistic Health Care? The science and art of medicine is in its infancy. Let us remain compassionate toward ourselves, as we are toward our patients.

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β-Lactamase Producing Haemophilus influenzae

To the Editor: This is a five-year follow-up report on the incidence of β-lactamase, producing *Haemophilus influenzae* type B (*H influenzae* B) organism isolated from the spinal fluid of children treated at Children's Hospital of San Francisco (CHSF) for meningitis.

From 1970 to December 1975, there were 34 children with *H influenzae* B meningitis treated with ampicillin (300 to 400 mg per kg of body weight). All had repeat lumbar punctures showing sterilization of spinal fluid after therapy was completed. One death occurred in 1973.

Isolation of *H influenzae* B with β-lactamase production and resistance to ampicillin were reported in 1974 and 1975. CHSF began testing all *H influenzae* B cultures in 1975, and during the spring isolates from children with pneumonia and otitis media were noted to be β-lactamase positive.

Since 1975 all *H influenzae* B cultures from children with serious illness, including meningitis, were tested for β-lactamase production by the tube dilution method. In the spring of 1975 a policy was instituted at CHSF to treat all life-threatening infections suspected to be caused by *H influenzae* B with both ampicillin (200 to 400 mg per kg of body weight) and chloramphenicol (100 mg per kg) given every six hours for 10 to 14 days. After the cultures were obtained, if β-lactamase production was noted, ampicillin therapy was discontinued and the child kept on a regimen of chloramphenicol or if nonproduction was noted, only ampicillin was given. In December 1975, the first child with *H influenzae* B meningitis resistant to ampicillin was identified.

There have been 38 cases of *H influenzae* B meningitis from December 1975 to April 1980. Five isolates of *H influenzae* B were found to be β-lactamase producers with ampicillin resistance. These five cases represent an incidence of 13.2 percent resistant organisms from the meningitis cases. All five of the children were treated successfully with chloramphenicol.

The results of the last five years support the policy of all severe cases of suspected *H influenzae* B infections (meningitis, periorbital or facial cellulitis, epiglottitis, septic arthritis or osteomyelitis in the appropriate age groups) receiving as initial therapy ampicillin and chloramphenicol.

There have been no isolates of *Haemophilus influenzae* B from children at CHSF with serious infections that are resistant to chloramphenicol. Such cases have been reported in the literature and a case of meningitis with resistance to both organisms has been noted. Therefore, all isolates of *H influenzae* B from children with meningitis should have full sensitivity studies.

A review of all cases of meningitis in children treated at CHSF in the last decade is being prepared.

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Refer to: Watts MSM: Orthodox medicine, humanistic medicine, holistic health care—Themes and thoughts from a forum. West J Med 133:351-355, Oct 1980

Orthodox Medicine
Humanistic Medicine
Holistic Health Care

Themes and Thoughts From a Forum

MALCOLM S. M. WATTS, MD

BEGINNING WITH THE DECEMBER 1979 issue and continuing through August 1980, the *WJM* has conducted a forum for dialogue and discussion of orthodox medicine, humanistic medicine and holistic health care. The forum was initiated with statements by persons known to have an interest in and knowledge of this subject, and readers of the journal were invited to submit their views constructively and succinctly. Many did so, and the discussion has been stimulating and, the editors believe, thought provoking for physicians and others interested in this subject. The promised summary, presented here, will focus on some of the themes and thoughts that emerged in the forum. Both published and unpublished materials were used in its preparation.

Wholism* and Medical Practice

There is substantial agreement that concepts of the whole patient have been part and parcel of medical practice "since the first shaman beat his drums." Hippocrates, Galen, Paracelsus, Avicenna, Maimonides, Osler and most recently Ingelfinger, orthodox physicians who together span the recorded history of medicine, all espoused the concept that physicians should consider patients as whole persons and indeed this is and continues to be traditional for orthodox medicine.

Beginning in the 18th and 19th centuries the mind, body and spirit began to be treated separately—with psychiatry treating the mind, medicine the body and clergy the spirit. As medical science developed, particularly in the 20th century, medicine has further divided the body and the treatment of its ailments into many specialties and subspecialties. Since World War II a whole generation of physicians has developed for whom the role models have been physician specialists in one or another of the differentiated branches of medical science. As curing became more possible, caring became less personal, and too often received less of these increasingly busy physicians' time and attention. And now it appears that a reaction has begun. In medicine it started with the students who in large numbers began to seek training in primary care of the whole patient, with emphasis on the caring function. This seems to be much more than a passing fad. It has already brought about significant changes in medical education and bids fair to influence medical practice profoundly. Meanwhile public perceptions were that scientific medicine had developed to the point where curing was to be expected and that if it did not occur something had to be wrong. Disillusion occurred when it turned out that scientific medicine did not assure health and that much of orthodox medical practice seemed to be losing the ability to make people even feel better. A result is that many people are now seeking care and comfort from alternative approaches, and physicians are increasingly being held liable in court when patient or public expectations of care are not fulfilled.

The pendulum has clearly swung too far, but it is starting to swing back. A new generation of physicians is looking more to the whole patient, and there is a new and growing emphasis on helping patients to achieve health, well-being and quality of life by coordinating the forces of mind, body and spirit. But there are clearly dangers in the present situation. The rubric of humanistic medicine and holistic health care may lure an

*Throughout this article the spellings *wholism* and *wholistic* appear in some instances and *holism* and *holistic* in others. This is purposeful, the intent being to use *wholistic* where the reference is to orthodox medicine and *holistic* when discussing the movement called holistic health care.

unwary physician beyond what is known through experiment and experience, and beyond a professional commitment to suggest interventions that are superior to alternatives and that have a value outweighing the risk. For the public the rubric of humanistic medicine and holistic health has too often provided a tent or umbrella under which slick-talking entrepreneurs can prey upon the resources of the ill, unhappy and dissatisfied; cultists can promote undocumented and unsubstantiated beliefs; and faddists can follow fashion or create their own. Both public and profession should beware of charlatans who advertise as holistic healers without any special qualifications.

Wholism has never been lost in medical practice but there has been a shift of emphasis that has been quantitative but not qualitative. There is need to restore a better balance of caring and curing, and of the whole and the parts.

How Much Is Science and How Much Faith?

It has become somewhat of a tenet of orthodox (allopathic) medicine that its methods are scientific and that those of other systems are not, or at least are less so. It is more or less assumed that what is scientific or scientifically *proved* is correct, and that what is not, or has not been, is at the very least suspect. But when one examines the interfaces of orthodox medicine with some of what is called humanistic or holistic medicine things become somewhat blurred. Michael Halberstam in a recent editorial notes some complete reversals in the last 15 years in what had been considered scientific medicine. He cites the treatment of cardiogenic shock, congestive heart failure and diverticulitis as examples (Halberstam MJ: The world turned upside down—Vasodilators, high-fiber diets, and other heresies [Editorial]. Mod Med 48:11-16, Jun 15-30, 1980). This has to be a humbling commentary on the dependability and even the current correctness of anything in scientific medicine. Then too, much of what is accepted and practiced as orthodox medicine, which has been found by experience to work, has not and may never be proved scientifically. There is quite a lot of glass, as well as a lot of solid construction in the house that orthodox medicine builds for itself when it rests its case on *scientifically proved* treatments.

This raises the question of faith and its role in treatment. There is reason to believe that mind, body and spirit may all be somehow involved in this modality. The placebo effect is well known in medicine, but what is not known is how often this faith accounts for the beneficial effects of other treatments, whether administered by allopaths or others. Certainly it appears that many systems of treatment, whether of the mind, body or spirit, or whether orthodox or other, make effective use of this as yet unscientific modality, whether consciously or unconsciously. It may be that many if not most alternative therapies (which may not have been shown effective by scientific methods) depend in part or entirely on faith for their effectiveness. The danger is that it will be considered that the therapy, not faith, was the effective agent.

Alternative health care methods may be divided into four categories: (1) biofeedback and other autogenic techniques; (2) introduction of Eastern approaches to medicine that rely on stress balance and integration of mind and body, such as massage, meditation or Tai-Chi, for example; (3) sensory awareness, dance, visual arts, music, and (4) some more formalized systems such as chiropractic, homeopathy and acupuncture. Many holistic approaches are part of the practice of most physicians at present—methods dealing with diet, exercise, rest, relaxation or coping with stress, for example.

The scientific method is an important tool which historically has only relatively recently been introduced into medicine. It is the hallmark of orthodox medicine. Basically it asks for evidence or proof that something works under the scrutiny of objective review. The process is slow and has yet to be adapted for study of all the approaches to treatment of mind, body and spirit, and rational and scientific techniques have less than fully revealed how both the human and social organisms work. Should we do nothing while waiting for information from a cumbersome, if careful, scientific approach? Physicians have always been open-minded about alternative methods, but do ask for objective proof or evidence that they work in the objective review of science. Orthodox physicians also oppose charlatans, cultists, faddists and others who would take advantage of the sick or distressed unwary, and will continue to do so.

Reductionism and Wholism

Reference was made earlier to the differentiation that has occurred in what originally may have been a more wholistic approach to care and

cure. The separation of mind, body and spirit did not separate the need to prevent illness (mind, behavior), to relieve disease (body, medicine) or to develop the fullest health (spirit, quality of life) even though the therapeutic approaches fall into separate hands. The scientific approach with its heavy emphasis on linear causation developed a scientific method that was heavily reductionist, focused more on the parts than on the whole, and had the effect of dividing scientific medicine into an ever greater number of technological subspecialties. It even began to pit man against nature and spoke of magic bullets and the conquest of cancer.

But there is reason to believe that there is more to medicine than is revealed by the rational scientific reductionist approach founded on the concept of linear causation. It is suggested that there is a need to look further and to examine alternative ways that have worked well for some people in the marketplace of patient care. It is noted that sometimes scientific rational support has been found for techniques previously considered irrational or nonrational. One contributor to the forum cited the philosopher William James as saying that orthodox institutions react to new theories first by attacking them as absurd, then admitting them to be true but obvious and inconsequential, and finally by considering them to be so important that the orthodox institutions claim to have discovered them themselves.

In the holistic view, disease processes should be understood in a broader context than linear causation—that is, as resulting from interactions of multiple factors—and it is suggested that this emphasis on multiple causes and multiple treatments is new. But rather than being content with either linear causation or causation by interactions of multiple factors, some seek a unifying concept, and proponents of orthomolecular medicine see man as a biochemical system that can encompass linear and multiple causation as well as unite the mind, body and spirit into a single system. In any case one cannot help wondering if the scientific method, as we know and use it now, may not be too simplistic to solve the very complex problems of interactions of multiple factors.

Emerging Role of the Patient-Person

For whatever reasons, there is a new emphasis on patients as persons; as persons who have genuine responsibilities in their own care when ill, and in the maintenance of their own health when well.

Norman Cousins is quoted as saying that every patient carries his own doctor around inside him, but every experienced physician knows that many if not most persons, especially those who have pain or fear they cannot relieve, seek help from outside of whatever resources they can muster from within themselves. Often they are more like supplicants looking for a higher power to help them. Experienced physicians also know that in the final analysis all a physician can do is to use the knowledge and skills of medicine in its broadest sense to assist nature to repair the injury or heal the illness. Although the art of medicine has never found a place in the medical curriculum, good physicians somehow learn from precept or experience to incorporate major principles of humanism and wholism into this process. Even with the growing emphasis on patient responsibility in medical and health care, there is little doubt that modern medicine still retains a basic relationship with patients that is in the realm of the spiritual. A distinguished neurologist points out that faith or confidence is what underlies the placebo effect however it may work.

But holistic health encourages a transition away from patient dependency (which is sometimes fostered by traditional medical practice) and encourages self-reliance and responsibility, and even self-care. In this sense the holistic and consumer movements have much in common. There is a new recognition and support of a patient-person's right to determine what will be done with his or her own body, and the relatively recent legal doctrine of informed consent seeks to make certain that this is the case in patient care. A patient with a brain tumor requiring an operation for its removal may decline to have this done, with or without the advice of any holistic healers, depending on how he views the process and the likely outcome. In fact the trend is toward individual freedom of choice of treatment whether this be conventional or otherwise.

When one moves on into the realm of health maintenance and prevention, the patient-person is beginning to be assigned a new and much more responsible role. To fulfill this role patient-persons need to be taught to assume responsibility for themselves and to achieve or maintain health through modification of unhealthy attitudes, values, habits or life-styles. It is here that medicine and the holistic health movement share much

common ground, and indeed these measures can contribute a larger positive effect on a patient-person's health, well-being and quality of life than does most caring and curing. What is true for patient-persons applies equally to the health of the public, and may also be true for society as a whole when it attempts to interact with a variety of genetic and cultural heritages.

Interfaces of Health, Environment and Illness

The contemporary system of medical care in the United States is one of detection and cure. It is not particularly geared to prevention of disease or promotion of health. In a sense there has been a gap between the treatment of disease and the promotion of health. Prevention and perhaps rehabilitation or restoration are at the interface between illness and health and are recognized specialties of medicine but so far relate more closely to illness than to what might be called wellness or health. In recent years programs to teach medical students, patients and the public about health have come into being and gained support. Also at this interface is the question of whether prolongation of life is an end in itself and whether health is a goal in itself or whether these merge with questions of what is health for and the concept of quality of life. It was noted that the answers to these questions differ among patients and persons (and among doctors) and the role of the healer is to help the patient or person to achieve his or her own goal.

If health is thought of in terms of a sense of well-being, of the good life and of the totality of existence, then the problems of the human organism merge with the problems of *organism earth* or the environment. It was suggested that behind most of the holistic dialogue lies an awareness that we cannot separate the internal from the external environments. At this interface health becomes a synthesis of the internal and external environments. Carried further, holistic means integration of all parts of the whole with health and illness as part of a continuum from the molecular to the ecological. And experienced physicians certainly know that bodily or mental states (will, spirit, life force) can at times tip the balance between health and illness, and even between life and death.

So the interfaces of illness, health and environment, and around again to illness when there is a disruption of balance between internal and external environments, seem to be shared by orthodox medicine, humanistic medicine and holistic health care, although at present each may place greater emphasis on one or another of these interfaces.

Social, Economic and Political Factors

Social, economic and political factors were important in the development of orthodox or allopathic medicine to a position of dominance over other systems of medicine, and social, economic and political factors are now contributing to the growth of humanistic medicine and holistic health care, and to the resurgence of strength among a number of nonallopathic systems of medicine. In California at least, holistic health has become a political movement with real political leverage, and with objectives that are political as well as therapeutic.

Beginning in the last century this nation began to develop what has become an elaborate medical care delivery system as a means of improving health. The reasons were probably more social, economic and political than therapeutic. As the health care system evolved, socioeconomic factors began to drive a wedge between doctors and their patients, and as the system became more costly many physicians could no longer afford to practice wholistic medicine; furthermore the socioeconomic problems of the nation began to be blamed on medicine by a public that had become disillusioned and frustrated. However, the political, economic, social and cultural strength of orthodox medicine and the commitment to a health system to improve health both continue, and it is unrealistic to expect that holistic practice will overcome orthodox or allopathic medicine, but there is reason to expect that because health policy responds to pressure, opinion and belief, a larger portion of the health care dollar will be allocated to the behavioral and environmental aspects of health. This has already begun.

Medicine at a Crossroads

It seems that what we have called orthodox medicine may be at a crossroads. It can follow its reductionist scientific approach to its logical conclusion, at which point physicians would become simply technicians skilled in the use of medical science to treat or cure illness or injury attributable to a specific biological cause. Or it can continue to embrace the whole in the tradition of Hippocrates, and develop whatever disciplines or methods that are necessary to be physi-

cians to persons or to society in a more wholistic sense of persons or societies interacting with each other and with what one contributor to the forum called "organism earth."

It may be that doctors and patients have different ideas about the role of today's doctors. Physicians trained in the reductionist scientific approach to patient care often tend to see their role as somewhat cold, scientific and even impersonal, whereas patients may need and expect something more than this to make them feel better. The science and socioeconomics of medical practice have made enormous demands on a doctor's time and the priority has gone more to what is in doctors' heads than what is in their hearts, and too often caring has been superseded by doing. Then there is the question of how much can be taught and how much can be learned in medicine and how far does medical practice extend beyond the treatment of specific illness, injury or emotional disturbance after it has occurred. And if medical practice is to become more wholistic, then will the theory and methods of linear causation be adequate to make wholism scientific or will other scientific methods and approaches need to be found and applied? These are some of the problems to be addressed by orthodox medical practice at the crossroads.

There is a considerable amount of wholism in medical practice today. One aspect of holistic health care is that the therapist and the client or patient view the problem from the same perspective and often consider a variety of approaches to treatment. This is done in orthodox practice as well, but it does take time and it does require the bridging of cultural and linguistic barriers between doctor and patient. It is noteworthy that the legal doctrine of informed consent requires that all options be disclosed and discussed with every patient. It is also noteworthy that birthing in orthodox medicine is becoming much more holistic in its approach and the very recent hospice movement is bringing many more holistic concepts to care at the other end of the life-span.

Thus it would appear that while the reductionist linear causation approach of today's medical science may be pushing physicians toward a role of medical technician, there are other forces and other traditions that view orthodox medical practice in a broader more wholistic perspective, and these are also very much alive in today's medical practice.

How to Go

It was suggested by many contributors that there be a reaffirmation of Hippocratic and Oslerian principles, that all of medicine is one and that physicians should play a leading role in its development and application. It is probable that neither orthodox medicine nor holistic health care fully understand the other approach, in fact there is some of each in both. It is necessary to separate out quackery wherever it exists and to document the effectiveness or ineffectivenss of improved treatment methods. It may be necessary to develop better research methods and research tools to address systems where many interactions are taking place almost simultaneously. The role and mechanism of faith, spirit and will in health and illness need more study and greater understanding.

One contributor identified the following as the great needs today in the field of health and medicine:

- To continue scientific advances in the basic medical sciences and indeed in all aspects of medicine and health;
- To establish a proper balance of the science and the art of medicine in keeping with the long tradition of medicine;
- To encourage the education of all people, and particularly children, as to their own personal health, and their personal responsibilities to attain and maintain it through proper nutrition; the development of a healthy attitude toward themselves and life; proper exercise, rest and relaxation; avoiding harmful agents as much as possible, and establishing periods of freedom from tension.
- To make available to everyone at reasonable cost and with easy access, medical and health care of high quality.

Refer to: Weaver C, Sklar D: Diagnostic dilemmas and cultural diversity in emergency rooms (Health Care Delivery). West J Med 133:356-366, Oct 1980

Diagnostic Dilemmas and Cultural Diversity in Emergency Rooms

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Language and cultural beliefs play an extremely important role in the interaction between patients from diverse cultural groups and physicians. Especially in emergency rooms, there are many dangers in missed communications. A patient from a foreign culture, especially one who does not speak English, often expresses symptoms in ways that are unfamiliar to many American physicians. Specific areas of cultural vulnerability can be identified for the major ethnic groups in the United States as they interact with the scientific medical system. A short review of folk medical beliefs and recommendations for improving diagnostic accuracy and treatment may assist emergency room staffs in offering care that is culturally acceptable to patients of diverse ethnic backgrounds.

EMERGENCY ROOMS have become the primary entry point into the Western medical system for a large proportion of the American population.[1-3] In our major urban centers, emergency rooms function to a great extent as a triage referral system to outpatient clinics, hospitals, laboratory services or neighborhood health clinics. The populations that especially use emergency rooms for nonemergency conditions are low economic groups,[4,5] newly arrived immigrants, members of minority ethnic groups, working-class and lower-class whites, and persons marginal to society. Even in the absence of economic constraints, hospital emergency rooms may be preferred over the offices of private physicians due to the "dis-ease" that often characterizes social contact between subcultures—in this instance between a middle-class white physician and a patient from a different social class or ethnic origin.[6,7] *Subculture* denotes the existence of a social group "that either does not hold all of the beliefs and values of the larger culture or accords them different emphasis."[8]

Emergency room physicians have the difficult task of providing medical care to patients who often belong to a different cultural world and who speak a different language from theirs. In an emergency room, rapid communication is critical to proper patient care. Communication difficulties due to linguistic or cultural barriers interfere with this process and unless physicians are sensitive to

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the role that culture plays in health and illness behavior patterns, serious mishaps may occur in this setting.

This paper explores the relationship between culture and medical belief systems as they are expressed mainly through language, and focuses on the role of communication in the interaction between physician and patient in emergency rooms.

Culture and Medical Belief Systems

Culture refers to a social group's "design for living." It is "a shared set of socially transmitted assumptions about the nature of the physical and social worlds,"[9] the goals and meanings of life, and the appropriate way of conducting oneself. Part of every culture includes ideas about body image and anatomical functioning, disease causation, symptoms, diagnosis and appropriate treatment, as well as prevention of disease.[9-12] Cultures differ in their medical belief systems, so that often what is perceived as illness, its causes and the appropriate treatment vary widely from one social group to another.

When members of one culture provide health care to members of a different culture, conceptual misunderstandings often occur.[13-15] The needs or expectations for both parties in the exchange are often either not understood or not mutually shared. The result is that the patient does not receive the type of medical care appropriate to his or her world view, and physicians are blocked in their attempts to provide care in a way that meets their own professional and emotional needs.

Cultural Differences and Emergency Room Care

An encounter between a patient and physician in an emergency room is characterized by the physician's attempt to separate potentially life-threatening illness from nonacute or chronic problems, and the patient's attempt to convey his perception of the urgency of his condition so as to receive prompt assistance. A pediatric patient represents a variation of this patient-physician interaction, in that the parent usually presents the complaint, provides the medical history and then judges the merits of the prescribed treatment. Except in obvious trauma cases, the physician depends on the patient's (or parent's) ability to explain what is wrong, where it hurts, the type of pain involved, and the like, to allow for an accurate and rapid assessment of the problem. Physical examination and laboratory tests are guided by this history-taking and serve to confirm suspected diagnoses. An omission or curtailment of the exchange of information as often occurs when a physician and a patient differ linguistically and culturally, forces the physician to emphasize physicial examinations and laboratory tests before having a clear idea about possible diagnoses. The following cases illustrate some of the misperceptions that occur in cross-cultural encounters in emergency rooms.

Reports of Cases

CASE 1. A 50-year-old Mexican-American man, who spoke only Spanish, was seen because of chest pain. No translators were available and, therefore, the English-speaking physician was able to obtain only a superficial idea of the direction, character or intensity of the pain. An electrocardiogram (EKG) showed no abnormalities, and an x-ray study of the chest disclosed widening of the mediastinum. The diagnosis of possible dissecting aortic aneurysm was made and followed with an aortogram for confirmation. The aorta was found to be normal. At this point, a Spanish-speaking physician entered the case and found that the patient had had difficulty swallowing and had been regurgitating food for the past year. A barium swallow study showed a massively dilated esophagus, and the disorder, achalasia, was finally diagnosed.

The lack of communication caused medical personnel to emphasize an abnormal finding on a diagnostic test (x-ray study) in the absence of an accurate history, subjected the patient to an unnecessary and life-threatening diagnostic test, and delayed proper diagnosis and treatment. Before conducting any diagnostic procedures that carry a potential risk to a patient, physicians should exhaust all possible means of obtaining translation services. This may be as simple as using bilingual hospital personnel, or as complicated as calling on the local consulate, an ethnic restaurant or a friend of a friend. In the event of an absolute absence of translation services, we recommend that emergency room staff have a series of flash cards prepared with questions and a list of possible responses.

Not only do language differences interfere with the medical treatment process, but they also block the social interaction between patient and physician. This interaction meets the social and emotional needs that are specific to the respective physician and patient. For the patient these needs

include having a physician treat him in a courteous yet professional manner that expresses concern for his condition and denotes technical expertise. The level of a physician's technical expertise is evaluated by his ability to explain what is wrong, why it went wrong and what must be done to effect a cure—all in concepts that are consistent with the patient's ideas of how a disease is caused. Through this ritually prescribed exchange of communication, the patient has his condition diagnosed and named, thereby reducing the anxiety aroused by the uncertainties that illness represents, and receives reassurance that a knowledgeable, competent healer will effect the appropriate cure for this illness. Thus, the possibility of direct verbal communication for the patient provides two essential ingredients for recovery: it removes the uncertainty of the unknown and it instills an expectancy for recovery.[16,17]

For a physician, verbal communication allows for a direct evaluation of the patient's complaint as expressed in his own words, and makes it possible for the physician to receive from the patient messages of trust regarding his medical expertise and gratitude for his help. Direct face-to-face communication also reassures the physician that the patient's complaints and concerns have been accurately evaluated and understood, meeting his professional needs to make a correct diagnosis and to help his patient. In the absence of verbal communication, part or all of these needs for both parties may go unmet, making this social interchange frustrating and a cause of anxiety for both the patient and physician.

Case 2. A 22-year-old Vietnamese man was brought to the emergency room unresponsive and comatose, with small reactive pupils. After there was no response to administration of naloxone hydrochloride (Narcan) and 50 percent dextrose solution, an intravenous line was placed. A history was obtained from the family, one of whom spoke English.

Interview

MD: Has the patient been sick?

Relative: Oh, very sick.

MD: Before, not just now?

Relative: Very sick.

MD: Does he have fever?

Relative: I don't know.

MD: Does he take medicine?

Relative: Yes.

MD: What does he take?

Relative: Pills.

MD: What kind of pills?

Relative: I don't know.

MD: Anybody else sick?

Relative: No.

This history-taking was being conducted with extreme urgency by the physician who had the difficult task of evaluating the underlying cause of coma in a young man. Through his questions he was attempting to rule out possible meningitis, drug overdose or toxins.

For Asians with minimal English skills, it has been our observation that their description of an illness usually is given in broad, all-encompassing terms: "very sick" or "hurt all over." It is not that they lack the criteria for making this evaluation, but rather that their manner of relating the story in their native language differs from Western medicine's conceptual categories. Added to this is the difficulty of communicating in a second language under stressful conditions. A trained, bicultural translator can effectively elicit the history as conceptualized by the patient or family, and translate it both linguistically and in the format of Western medicine.

As it was in this case, the history given by the family member gave no hint toward a direction for further diagnostic tests. A spinal tap ruled out meningitis, leaving the obscure diagnosis of "metabolic coma of unknown origin." Fortunately, during the admitting process, an astute clerk noticed that the patient's name was the same as that of a child admitted the day before with headache, nausea and vomiting. A carboxyhemoglobin study was done subsequently on the young man and levels were found to be substantially elevated. A diagnosis of carbon monoxide poisoning was made and oxygen therapy was begun. A public health nurse visited the patient's house and found a defective heater, as well as three other symptomatic family members. The heater was fixed, and the patient recovered with no residual neurological difficulties. However, except for the observations of the admitting clerk, this patient's prognosis could have been much worse, and other family members could have died.

Case 3. A 53-year-old Navajo woman came to the emergency room because she felt that she was

having difficulty in breathing. She did not appear distressed and was not complaining, and therefore was sent to the main waiting room. The patient did not protest the request to wait and did not indicate any sense of urgency. The woman spoke no English but brought with her a Navajo interpreter who stated simply that the patient was generally healthy and "drank a lot." The workup process started approximately an hour later when the triage nurse ordered an x-ray study of the chest, which showed no abnormalities. In the physicial examination, chest auscultation produced wheezes even in the mainstem branch, and an examination of the throat showed a pseudomembrane extending over the tonsils and down the trachea. Her airway was severely compromised. The examining physician's reaction was "Why didn't she say something?" Only with specific questioning did the patient admit to having a sore throat; left to the patient, the only symptom she had perceived was that it had become hard for her to breathe. Despite an immediate emergency tracheotomy and administration of diphtheria antitoxin, a cardiac arrest occurred within 24 hours and the patient died.

The emergency room staff's reaction was one of extreme frustration, feeling that the patient had "let the staff down" by not alerting them to the urgency of her condition. Indeed, according to the staff's expectations, the patient had not conducted herself according to the "sick role" definition[18,19] that they held.

This case illustrates cross-cultural differences in what is recognized as illness, the perception and reporting of symptoms, and varying degrees of tolerance of pain and discomfort.[20-22] The Navajo woman perceived only the symptoms of labored breathing among all those that accompany the serious respiratory infection of diphtheria. History-taking in this case would require asking questions about specific symptoms (for example, "Does your throat hurt now?") as opposed to questions regarding broad systems, such as "Besides your breathing, do you have any other problems?" Also, an untrained translator often shares the same conceptual world as does the patient,[23] and, consequently, cannot be expected to provide information that is essential to the diagnostic evaluation without specific and simplified instructions from the physician.

Case 4. A 37-year-old Mexican-American woman was brought to the emergency room with the chief complaint that a frog had been placed in her stomach through witchcraft. The examining physician concluded that the woman had a psychotic disorder; however, a friend accompanying the patient explained through a bicultural interpreter that indeed the patient had been bewitched and that only by breaking the witch's spell could the frog be removed. The prescribed treatment for this illness lies outside the belief systems of Western medicine. Western medicine does not recognize the deleterious wishes of others (witchcraft) as a causative agent of disease pathology. Consequently, it lacks explanations and treatments for this category of illness, which is a part of the Mexican-American medical belief system. Thus, the patient was referred to a local *curandero* (a traditional healer in the Mexican folk medical system) known to one of the emergency room physicians, and the *curandero* successfully worked a spell to break the witchcraft's power. The patient reported that with this treatment the frog immediately left her, and she went on to have an uneventful recovery.

The prescribed treatment given by a *curandero(a)* combines medical-spiritual power for healing, counseling, the performing of religious prayers and rituals, and the administration of herbal remedies. Patient participation is also required in some way, so that he or she is included as an active participant in the recovery from illness. In the above case, the folk practitioner acknowledged the legitimacy and validity of the woman's complaint, performed the appropriate curing ceremony and offered advice on how to conduct herself in the future so as to avoid these problems. Just as a physician offers technical expertise to diagnose and treat disease according to the cultural beliefs of Western medicine, so too, the *curandero* does so according to the medical beliefs of Mexican culture. In both systems, the medical practitioners effect the same expectancy of a cure and instill in their patients the all important feature of hope—a strong belief that now they will get well.

Case 5. An 8-month-old Jemez Indian infant was brought to the emergency room by his 17-year-old mother because the baby "felt hot" and was "sick." She was unable to add anything further to her description of the baby's illness. The infant was still feeding well, and findings on physical examination were unremarkable except for a temperature of 38.9°C (102°F) taken rectally. An x-ray study of the chest showed no abnormalities, and the impression of the emergency

room staff was that an upper respiratory infection was present; therefore, a decongestant was prescribed. The mother was instructed to bring the infant back if his condition worsened. Three days later the baby was brought back to the emergency room comatose with a bulging fontanelle; *Haemophilus influenzae* was seen on a Gram-stain of a cerebrospinal fluid specimen. The mother explained that the child's condition had become worse the next day, so she had gone to a native healer who had given her a "native medicine" and chanted a prayer over the baby. The following day the baby was fitful and was not feeding. She felt that both medical systems had done their best and that now she must wait for the cure. On the third day, however, the baby would not wake up, which frightened the mother into returning to the hospital. The child recovered but had recurrent seizures thereafter.

This case illustrates a principle seen in several cultures—the idea that a doctor's first therapeutic modality should be immediately successful or else nothing can be done. Recognizing this belief helps in understanding the reluctance of Native American, Mexican-American, Chinese and Filipino patients to return for further medical treatment. Many cultural groups lack a concept of chronicity of illness states, and thus expect one herbal treatment (or hypodermic administration of an antibiotic drug) to effect immediate results.[10,24] They may also look on a failure of the first treatment regimen as a loss of face for the physician, should it be brought to his attention; therefore, they are reluctant to embarrass him and themselves by returning.[25]

To avoid the situation in which a patient will not return after the first prescribed treatment has failed, a physician may wish to qualify the efficacy of the medication. An explanation of the process and course of the disease that is appropriate to the patient's cultural beliefs and educational level should be given, as well as encouragement to return in a few days for a different medicine should the patient's condition grow worse. This leaves the door open for further contact without placing fault for failure on the physician or the patient.

In the case above, the emergency room physician should follow the progress of a (cross-cultural) pediatric patient, who presents with a vague febrile illness, with a phone call when possible to verify that the child is responding to treatment. If outreach workers are available, they may be used to make home visits when telephoning is not possible. In emergency room settings, diagnostic dilemmas often clarify themselves over the ensuing 24 hours, and a physician can make the diagnosis if he encourages the patient to return. A translator, when available, can help to explain that the physician wants the child to return if his condition worsens, as well as being able to explain what constitutes worsening. And finally, a liberal admitting policy with respect to patients who may not comply with the physician's plan is particularly applicable in cases where cultural restraints may make a revisit unlikely.

Case 6. A 22-year-old black woman was admitted for a shotgun wound to the chest and left arm. The young woman had been wounded when the mother's boyfriend, outraged by her request to end their relationship, had shot through the family's front door. The wounded daughter was the youngest in a family of six. The incident left the family violently angry at the offender, and extremely anxious over the welfare of the patient. Shortly after the patient had been brought to the trauma unit of the emergency room, immediate and extended members of her family arrived, totaling 18 adults and several small children. The nursing staff had difficulty restricting the large number of family members to the waiting room, and they were too numerous to fit into the small family room. Family members stood about in the hallways and around the nurses' desk, while the two sisters alternated between visiting the patient and keeping the family informed.

The family members talked in a loud, excited manner punctuated with angry outbursts as they discussed the appropriate actions to be taken against the offender. On receiving a report from one of the sisters that the physicians were considering having to amputate the patient's left arm due to severe circulatory impairment, the family became agitated, with one sister screaming and crying uncontrollably. One trauma staff nurse started yelling repetitively "Out! Everyone out!" She simultaneously started pushing the sisters out the door. Pandemonium spread quickly and the family members refused to leave. Security guards had to pull one of the sisters away from a physician who had attempted to reinforce the nurse's order; the fracas ended when the security guards physically escorted the family outside the emergency room doors. The family was kept there by posted guards until the patient was sent to surgery. The functioning of the emergency room was totally disrupted for the duration of the incident

and for hours afterwards while the staff recovered their equilibrium. The staff concluded that the family's behavior revoked their right to receive care at that institution in the future.

In interviewing one of the family leaders (the oldest sister) days later, the woman explained simply:

> That's the way we are. If we are upset, we show it! We don't keep it inside like white folk; we let it out. And when we all together, we loud.

The major reason why things had gone wrong from her perspective was that the emergency room staff had failed to attempt any kind of contact with the family, other than to issue directives. The family felt that they had been treated discourteously and insensitively by a white medical staff. As it was, no trust or rapport had been established between the providers and the family, the result being a highly unsatisfactory exchange, with poor communication and misunderstanding. The family leader suggested that if a nurse or physician had simply appointed a contact person through which they could transmit information and direct rational requests to the family, most of the ill feelings and the altercation would have been avoided.

The importance of the extended family for many ethnic groups requires that emergency room staffs learn techniques for managing communication with large groups in trauma situations. One recommendation is to ask the group for a representative, through whom the staff can channel information and answer questions. This leader also can be made responsible for managing the family according to the staff's need for privacy and quiet in the emergency room. Thus, directives will come from the recognized, legitimate family leader, and not from medical personnel who run the risk of lacking the recognized authority to give orders.

Discussion

In the foregoing case reports we illustrated some of the dangers of missed communication involving language and world views that occur in emergency rooms, and recommended actions that may help to minimize these pitfalls. Without such intervention, diagnoses can be delayed and needless morbidity and mortality may occur. Current increases in immigration due to a relaxing of the quotas that were in effect before 1965 and the recent influx of political refugees from Southeast Asia and Central America, give this problem an impelling immediacy in many areas of the United States.

As our case examples show, language is essential to a physician's ability to diagnose and treat patients accurately. In the instance of patients who do not speak English the curtailment of clear communication often leads to incorrect histories being taken, which results in incomplete or missed diagnoses and equally limited treatment. Translators may help as well as hinder the communication process. Most translators used in emergency rooms are not trained for that role, but are either recruited from other areas of the hospital or are family members or friends of the patient. The latter may obstruct a physician's effort to obtain an accurate history by interposing their own interpretation of the question or answer rather than directly translating because they are not objective and because they are not familiar with medical terminology and hospitals. Furthermore, in their presence the patient may withhold embarrassing information. In addition, the time needed for three-way communication can be prohibitive in emergency situations, unless a trained, highly skilled translator is used.

San Francisco General Hospital instituted a translator training program and translator pool for their multiethnic patient population in April 1978. A study is in progress that chronicles the impact of trained translators on the delivery of patient care. From preliminary findings it appears that trained translators facilitate the delivery of accurate and efficient medical and nursing care, as well as increase patients' satisfaction and help them to use hospital services.

In our case reports, no translation or a poor translation of the history can be directly blamed for the uncertainties of diagnoses in the first two cases. The presence of even an untrained translator might have helped. However, in the next three cases translation was available, and in case 6 the language was the same, but a breakdown in communication still occurred. These are examples of cultural misperceptions in which language is only a part of the process of communication.

Diagnostic Problems Associated With Specific Cultural Groups

Each social group has areas within its culture that make it vulnerable in its interaction with the Western medical system. We identify sev-

eral below to alert physicians caring for cross-cultural patient populations.

For Spanish-speaking cultural groups, there exist several, specific disease syndromes that are not recognized as disease entities in Western medicine. A patient who presents with symptoms he believes are consistent with a known folk syndrome expects the physician to acknowledge this, and either confirm or dismiss his home diagnosis. The physician need not agree with his patient's belief system, but only acknowledge it in a nonjudgmental manner. After the diagnosis has been discussed, the patient will often expect specific dietary instructions in conjunction with medications as the prescribed therapeutic regimen. Specific areas to be mentioned include the use of hot or cold drinks, alcohol, coffee, chili and medications that the patient may already be taking.[26-28] A common belief is that two medications taken together will cancel each other out, or that a particular "hot" food may cause the disease to worsen. The role of diet in illness should be discussed even if the patient does not ask questions about it; this may be done by explaining that the patient may eat any food he has found to be helpful in the past, with the continuation of other medications being a medical decision.

The cross-cultural differences in behavior when a person perceives himself to be ill, specifically the manner of presenting symptoms, may present problems for physicians, particularly when working with Spanish-speaking patients.[29-33] Spanish-speaking cultural groups generally perceive more symptoms and present with a greater diversity of complaints in illness states than do cultural groups of western and northern European origin. Emergency room personnel are often perplexed in their attempts to diagnose the combination of symptoms presented by Spanish-speaking patients, and commonly interpret their complaints as an expression of emotional problems. While the tendency to express emotional states as specific disease entities or as physical symptoms is seen as legitimate within indigenous cultures,[10,14,26,34-38] it is viewed as illegitimate illness behavior within Western medicine. Such behavior is frequently characterized by emergency room personnel as psychosomatic, psychiatric, malingering, or faking, or as the patient just looking for pain medication.

In Asian cultural groups there are certain values commonly held that can be cultural pitfalls for an unaware physician. The strong emphasis on saving face and the importance of maintaining the family's good name are attitudes found among Southeast Asian, Chinese, Filipino and Korean populations.[39] The value placed on avoiding acts or situations that can bring shame or embarrassment, or cause shame to one's family strongly regulates social behavior in these groups even today.[25,40-44] In health care settings, the following situations may be viewed by a patient as producing shame: any reference that suggests that the person speaks poor English, or that he *should* be able to speak English; a physical examination in the presence of a member of the opposite sex or a pelvic examination of a girl who is a virgin; treatment of an elder without the proper degree of respect, or any expression of displeasure or irritation at the patient's health beliefs or behavior.

The giving and receiving of respect is a critical factor which governs social interaction for the East Asian groups.[45] A physician who anticipates and skirts areas of conflict will be more trusted by his patient than one who attacks and tries to resolve the conflict. Sometimes it may be necessary to enter an area of potential conflict. If so, the physician should acknowledge to the patient and family that he is aware of the problem, but then describe the risks of avoiding the condition (such as a pelvic examination of a virginal girl with vaginal bleeding). The physician may be able to gain the family's consent to do a specific diagnostic test, but should be aware that he or she is treading on dangerous ground and that the patient-physician relationship may be destroyed irreversibly.

Members of the Navajo and Pueblo peoples are particularly vulnerable in that they often fail to call attention to themselves or to emphasize urgency.[23,46,47] A calm, stoic attitude about pain may lull an unwary physician into underestimating the severity of illness. We have found at times that when a Navajo says he is weak he actually means that he cannot move, and when he says his belly aches it may really mean that his gall bladder has perforated. Patients from these cultural groups may also be unwilling to return if their conditions worsen, turning instead to a native practitioner unless the physician specifically advises them to return.

In addition to language and conceptual views about illness, differences in nonverbal communication may interfere with the flow of information between a physician and a patient. For example, the need for distance between persons as they

communicate varies between cultures.[48] A Filipino, Latin American or Arabic patient may feel that he needs to get closer to the physician when speaking than the physician is comfortable with, resulting in the patient edging closer and the physician edging away. Both participants may sense anxiety and tension in the interaction without knowing why.

The use of eye contact in communication also varies considerably among different cultural groups.[49-52] Anglo-Saxon Americans tend to use direct eye contact during both speaking and listening.[49,51] Watson (1970)[50] found in observing dyadic conversations that Arabs, Latin Americans and Southern Europeans focused their gaze on the eyes or face of their partner; whereas, Asians, Indians and Pakistanis, and Northern Europeans tended to avoid direct gazing. A comparison of American white and American black dyads reported by La France and Mayo (1976)[53] similarly showed less direct gazing among blacks for both homosexual and heterosexual dyads. In an earlier study,[54] these investigators found that while American whites look at the speaker, American blacks do not look while listening; they made the following conclusion:

> When blacks and whites interact, therefore, these differences may give rise to communication breakdowns. The white may feel he is not being listened to while the black may feel he is being unduly scrutinized.[54(p7)]

We cannot offer any strict rule of thumb to follow in these situations except to caution practitioners to be sensitive to their direct and nondirect gazing and its effect on patients of other cultural backgrounds. Too much gazing while speaking or listening may be regarded as superior, disrespectful, threatening or insulting by Africans, Asians, East Indians, American blacks and Native Americans[49-51,54,55]; and too little gazing, especially in telling the diagnosis and prognosis, risks being seen as insincere, dishonest or shy. Arabs and South American groups emphasize direct gazing in conversation and tend to equate lack of eye contact with being inattentive and impolite.[49,50]

Attention to time is another area of potential cultural conflict for physicians and cross-cultural patients.[23,48,55] Emphasis on the accuracy of time is most exact in the Anglo-Saxon American culture. Thus, a physician of Anglo-Saxon descent may expect ten o'clock to mean plus or minus five minutes, while a patient of Filipino descent may understand ten o'clock to mean ten o'clock plus or minus an hour. If an accurate assessment of time is important in the history-taking, an emergency room physician should question the patient or family members closely on their estimate of the time involved in the event, such as in cases of toxic ingestion.

Just as important to communication as language and nonverbal cues is the physician's understanding of the medical beliefs and practices specific to each group's culture. The following section is a brief summary of the principal concepts in the folk medical systems of the major ethnic groups in the United States.

Important Concepts in Folk Medical Systems

In general, folk medical beliefs divide the occurrence of disease into those having a *natural* cause and those having *unnatural* causes. The first category includes illness states attributed to imbalances in the body's natural, emotional or physiological equilibrium. Most traditional medical belief systems lack the rigid mind-body dichotomy maintained in our Western medical system's explanation of disease causation[56-59]; thus, folk medical systems often include an emotional, psychological and social component in their characteristically multicausal explanations for disease occurrence.[10,16,26,60-63]

For example, Arabic and Central and South American cultures recognize a disease syndrome which in Spanish is called *mal ojo,* or evil eye. Children are the most susceptible in that they are the most dependent and vulnerable segment of the population. The causative agent is a distant relative or stranger who admires a child without touching him or her. The diagnosis is based on a specific symptom complex and is treated by a mixture of religious rituals, magical incantations and physiological interventions.[10,26] The *mal ojo* illness has a natural explanation in these folk medical systems in that it is based on a belief in the vulnerability of the weak to those having a stronger physical and psychological makeup; this attitude also reflects their larger world view of the natural social order.

More basic to daily behavior, however, are all the disorders connected to the hot-cold balance theory found in Chinese, Arabic and Spanish-speaking cultures, in which it is believed that the body contains balanced quantities of humoral substances with hot and cold qualities.[24,64-68] Within this belief system, diet plays a central role

in maintenance of health as well as treatment of disease.

In the second category, unnatural causation, belong illnesses attributed to the actions of displeased spirits, god(s) or ancestors, or illnesses that result from the malicious intent of human agents through the use of witchcraft rituals.[34,62,67-74] Our current work in the San Francisco Bay Area has indicated a strong persistence in witchcraft beliefs among black and Spanish-speaking populations, and these findings have been corroborated by many other investigators including Maduro (1975)[75] for the San Francisco Bay Area, Garrison (1979)[76] for the Northeast Coast, Snow (1974)[62] for the Southwest area and Weidman and colleagues (1979)[77] for the Southeast coastal area.

More detailed description of the medical belief systems of the major ethnic groups is beyond the scope of this paper. However, an appreciation of the variation is essential to understanding the motivations and fears of patients who hold these beliefs, even when they seek aid from those practicing Western medicine. Often a patient is caught between the two worlds, believing his folk medical causes of disease, but viewing the physician's medicine as more powerful than his local healer's for certain types of illness. Although translation of language is often blamed as the culprit in an unsuccessful physician-patient interchange, it may actually be differences in beliefs about the causes of disease and its cure that bring about missed communication.

Recommendations

We make the following recommendations based on work with a multiethnic, multilinguistic group of patients in several San Francisco Bay Area hospitals. In regions where only one minority exists, these may need appropriate modification. The recommendations are geared toward *helping* physicians care for culturally different patients. Physicians already have the difficult task of being *all things to all* their patients, and the psychological and emotional toll that this takes is reflected in the high "social morbidity" statistics (divorce, alcoholism, drug addiction, suicide and the like) for physicians.[78-81] Thus, our first recommendation is to incorporate a person trained in medical social science on the hospital staff to assist physicians in an advisory, consulting and supportive capacity as they care for culturally diverse patients. We envisage this addition to the health care team as a "helper of the helpers,"[82] a cultural specialist[76,83] who can function as a cultural translator for both the physician and patient, thereby enhancing communication and the satisfaction of needs for patients and physicians.

Second, the hospital should include in its library a selection of works of the major medical beliefs and illness syndromes of cultural groups most served by that institution, as well as specific instructions concerning taboos about physical examination and diagnostic tests.

In urban centers where there are ethnic populations who do not speak English, hospitals should make use of translators who are bicultural and bilingual and who have been trained both in medical terminology and in the organization and functioning of the hospital. Such personnel represent a rich resource of anthropological expertise, of which physicians should take advantage. Translators are cultural brokers, middlemen between two cultural worlds—and if there is a good working rapport between translator and physician, the physician-patient interaction will benefit directly. Therefore, it is critical to establish a good working relationship with your translator and use him as the cultural expert that he is.

When translators are not available, a bilingual flash card system covering physical examination questions and possible responses can be used as backup to the translator system. A two-card system should be developed—one in which the foreign language can be written in phonetic English for the physician to read, and another in proper form for the patient capable of reading and selecting the appropriate response card. In small hospitals where employing trained translators may not be possible economically, a roster of bilingual staff members willing to volunteer their services as translators during their work hours should be compiled and updated every six months. In addition, these staff volunteers should be trained in the nuances of language as it applies to medical terminology and history-taking.

In predominantly non-English-speaking areas (for example, the Southwest and ethnic areas in urban centers such as San Francisco, Los Angeles, New York and so forth) physician language training programs should be instituted. Specific suggestions for handling language problems are as follows: If the physician and patient speak different languages but the patient speaks some English, the physician should ascertain whether the patient has understood his instructions by asking the pa-

tient to repeat the instructions back. The physician should be careful not to criticize a patient who shows his lack of understanding by not being able to repeat the instructions. Rather, he should again instruct the patient slowly, pronouncing clearly, in simple English and again conclude by asking the patient to repeat the instructions. If the patient is still unable to do so, the patient should be asked to wait until a translator is available to help before dismissing the patient.

In instances in which follow-up is questionable or diagnosis is uncertain, and the patient's condition is unstable, the physician should err on the side of caution and admit patients to hospital liberally. Also, it should be reemphasized to any patient sent home that he is requested to return to the same hospital emergency room if his condition gets worse, or if any new symptoms or circumstances develop. The patient should be encouraged not to feel embarrassed to return with the same condition.

Although the stresses of emergency room work often give rise to moments of comic relief when bizarre crises occur, one must be careful not to laugh at an already uncomfortable and frightened patient from another culture. He may misinterpret the laughter as a personal rebuke and either refuse medical care, ignore recommendations or feel so humiliated that future care is avoided.

The principle of presenting and delivering Western medical care in a way that is culturally acceptable to English and non-English-speaking patients holding beliefs of different medical systems is critical to the future practice of medicine in our increasingly pluralistic society. To establish the conditions basic to a successful healer-patient relationship, a physician must understand a patient's conceptualization of disease cause and treatment, and translate his actions and rationale in a way that is culturally compatible and acceptable to the patient.[13,84]

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Special Article

Avicenna and the *Canon of Medicine:* A Millennial Tribute

RICHARD DEAN SMITH, MD, *Walnut Creek, California*

ABŪ ALĪ AL-HYSAYN IBN-'ABD-ALLĀH IBN-SĪNĀ was born in 980 AD in Persia and became one of the most brilliant figures in the history of medicine, acclaimed the "Prince and Chief of Physicians." As a thinker, he represented the culmination of the Islamic renaissance. He was described as having the mind of Goethe and the genius of Leonardo da Vinci; through Hebrew transliteration of his name he is known as Ali ibn-Sina or Avicenna. Most famous as a philosopher, he was also a physician, mathematician, naturalist, geologist, musical theorist, astronomer and poet. He held the political post equivalent to prime minister as well. Dante acknowledged him in the *Divina Comedia,* and Chaucer in the *Canterbury Tales.*

The wealth and power of the Golden Age of Islam that began in the eighth century extended from the border of China to Western Europe. The growth of rationalism gave reason the highest importance in all but the most fundamental articles of faith. It was an age of superb architecture, fine pottery, beautiful silks, music and poetry; talent had free scope and ability was in great demand. Science flourished, making great advances. The professions were dignified—their members wore handsome academic robes and received liberal emoluments, thereby becoming leading and wealthy citizens. Such an age spontaneously creates great men, and Avicenna, while intellectually supreme, was one of many.[1-5]

Medicine attracted the finest and most distinguished personalities. Physicians were in great demand; they were honored and often greatly rewarded. Many hospitals were built with extensive services. Medical education supplemented the apprentice system with formal lectures, clinical demonstrations, group discussions and library research. An examining and licensing system for physicians was established in 931 AD and ethical standards were of the highest tradition of responsibility and integrity. Medicine held a strong attraction for a man of Avicenna's abilities.[5]

More is known of Avicenna than most ancient physicians from an autobiography of his early life, which was later continued as a biography by Juzjāni, a student and follower. By ten years of age Avicenna had memorized the Koran and most of Arabic and Persian literature, "and it was accounted a marvel." He mastered mathematics, astronomy, law and philosophy, and then turned his attention to medicine.

> Medicine is not a difficult science, and in a short space of time, of course, I excelled in it so that the masters of physic came to read with me, and I began to visit the sick. Consequently, there opened to me the doors of various kinds of treatment which I learned by experience. I was then about sixteen years of age. During the period of hard practice and study which then ensued, I never once slept the whole night through. If a problem was too difficult for me, I repaired to the Mosque and prayed, invoking the Creator of all things until the gate that had

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been closed to me was opened and what had been complex became simple. Always, as night fell, I returned to my house, set the lamp before me and busied myself with reading and writing. If sleep overcame me or I felt the flesh grow weak, I had recourse to a beaker of wine, so that my energies were restored.[6]

His father died when Avicenna was 21 years old, and at that point the autobiography ends. Later, Juzjāni continued describing Avicenna's life in his biography.

While serving as a vizier to the Amir of Hamaden he disturbed the army probably with his philosophical teachings, his house was plundered and he was forced into hiding where he worked on the *al-Qanun*. The Amir was stricken with colic, Avicenna was summoned, effected a cure, and he was restored to his office. Later, when the Amir died Avicenna was forced into a quick departure.[6]

Avicenna was a lonely, dissatisfied man who never married. He had a violent temper, with merciless scorn for the mediocre, disdain for conformity and a dedication to the search for truth. With a handsome and imposing presence, he could be charming and witty in conversation and a formidable adversary in debate. A man of immoderate and excessive passions, his days were passed with the affairs of state, practicing medicine and attending the Amir, while the evenings were spent enjoying music, poetry and wine until his guests were asleep or exhausted. Avicenna would then spend the rest of the night finding solutions to the most vexing problems of philosophy and metaphysics. When reproached on his excessive appetites and passions, he replied that he was interested in a life of the fullest breadth, not length, and said "God, who is exhalted, has been generous concerning my external and my internal faculties, so I use every faculty as it should be used."

Physicians in Avicenna's time visited the sick, paying particular attention to each patient's appearance and pulse, and examining the urine. A physician then prescribed a remedy for the patient and was required to give a copy of the prescription to the family. He continued to visit the patient daily and wrote new prescriptions according to his findings, which continued until the patient recovered or died. In the event of a recovery, the physician received his fee and an honorarium. If the patient died, the family took the prescription to the chief physician, officially appointed in each city. If the chief physician said the treatment prescribed was in accordance with the requirements of science and the art of medicine he declared that the person's life was ended by "termination of his allotted span." If he was of a different opinion he said, "exact the blood-money for your kinsman from this doctor, he slew him through negligence and lack of skill."[3]

Avicenna wrote numerous medical books, many in verse,[7] but the most famous was the *al-Qanun* or *Canon of Medicine* (Greek for standard).[8] It contains over a million words in five books titled: (1) General Principles of Medical Practice, (2) Simple Drugs, (3) Local Disease, (4) General Diseases and (5) Compound Medicines. Other comprehensive and systemic compendia of medicine had been written by Avicenna's predecessors, al-Rhazes (841 to 926), and Ali ibn-Ul Abbas (died in 994), but the *al-Qanun* was the final codification of Greco-Arabic medicine, and one of the monumental works of all times. The first four books were based on the principles of Galen and Hippocrates, with the addition of the teachings of Arabic physicians and Avicenna's own observations. The fifth book, a formulary of drugs, was a new Arabic contribution to medicine of inestimable importance. It became a classic as soon as it appeared, and was translated into Latin in 1175 and later into many other languages. The *Canon* finally lost its authoritative status in the 17th century in Europe when autopsies were permitted. Only the Latin translations were from the original Arabic, and are considered so poor that they do not reflect the stature or grandeur of the *Canon,* giving to the West a distorted version of Avicenna's teachings. In 1977 the Institute of the History of Medicine and Medical Research of New Delhi assembled a team of translators to develop an English translation free of errors, using the Istanbul manuscript of 1220 AD, the oldest extant manuscript of the *Canon*.[9]

The *Canon* states the following: "Medicine is the science by which we learn, the various states of the human body, in health, when not in health, the means by which, health is likely to be lost, and when lost, is likely to be restored to health. In other words, it is the art whereby health is conserved and the art whereby it is restored, after being lost." It describes the body's internal milieu and homeostasis, infectious causes of disease and transmission of disease by contagion, heredity, or racial or endemic factors; it also describes "auto-intoxication," psychotherapy and many other modern concepts of medicine.[2] Diseases were categorized according to their degree of heat, cold, dryness and moisture. The principle of

medical treatment was based on the Rule of Opposites:

If a disease originates from heat, it must be treated with cold, if from moisture, then with dryness, etc. If the cause is fear or grief, then the physician must induce tranquility and confidence in his patient, but first, the etiology of the disease must be understood; only then is it possible to begin treatment.

Avicenna's metier was classification, division and subdivision. For instance, in the *Canon* he described 15 types of pain: boring, compressing, corrosive, dull, fatigue, heavy, incisive, irritant, itching, pricking, relaxing, stabbing, tearing, tension and throbbing. In the chapter of sphygmology he described 10 features of the pulse and 22 types of abnormal pulses. In the chapter on urinoscopy great attention was given to the examination of urine—its quantity, odor, color, foam, texture, clearness and sediment, and diseases were classified accordingly.

Analgesic drugs discussed in the *Canon* are remarkably current.

The most powerful of the stupefacients is opium. Less powerful are: Seeds and root barks of mandrake [contains the alkaloid mandragorine, a narcotic and hypnotic]; poppy [morphine and papaverine]; hemlock [conium, an alkaloid that produces motor paralysis without loss of sensation or alteration of consciousness]; white and black hyoscyamus [hyoscyamine and scopolamine with atropine-like effects, cerebral depressant and sedative]; deadly nightshade [belladonna]; lettuce seed [hyoscyamus and mannitol]; snow and ice-water.

Wine served many uses including antisepsis in the irrigation of wounds. Avicenna comments in the *Canon:*

White wine is best for those who are in a heated state, for it does not cause headache. . . . Old red wine is best for a person with a cold, phlegmatic constitution. . . . Wine is beneficial for persons with a predominance of bilious humor, because it gets rid of the excess of this by provoking the urine. It is good for persons of humid temperament because it brings humidities to maturity. . . . If a gnawing feeling comes on after taking wine, take pomegranate, cold water, and a syrup of absynth next morning.[8]

He gave seven rules for a reliable experimental investigation of the effects of drugs in humans that are as stringent as today's standards. All drugs were considered to have the same four properties as disease—heat, cold, dryness and moisture.[2]

The first book devotes great attention to preventive medicine and good health practices are summarized in the "Essential Matters in the Art of Preserving Health"[8] as follows: (1) Equilibrium of temperament; (2) selection of the articles of food and drink; (3) evacuation of the effete matters; (4) safeguarding the composite; (5) maintaining the purity of the air respired; (6) guarding against extraneous contingencies, and (7) moderation in regard to the movements of the body and the motions of the mind, many of which may be "sleep and wakefulness."

Avicenna gave the following advice to the son of a prince, should he be reduced to earning his living by the practice of medicine.

Once you embark on a career as a physician, if you wish to gain experience and reputation you must experiment freely, but you had better not choose people of high rank or political importance as your subjects. To gain confidence you must see a great deal of service in hospitals, where cases of all sorts shall pass under your hands, and where you actually see for yourself what you have read in textbooks. With such training no disease, however rare, will present you with any difficulty and diseases of the internal organs will be no mystery to you. When you visit a patient in his house you must be clean in person and dress and agreeably perfumed. The expression on your countenance should be pleasant and you should go only when you are untroubled in spirit. The physician's encouraging words increase the potency of the warmth inherent in man's natural temperament.[3]

Avicenna was even more famous and influential in philosophy than in medicine and compiled philosophy in the *Kitab al-Shifa* (The Healing). Avicenna's approach to reconciling Aristotelian philosophy with the Moslem religion made it possible in later centuries for similar efforts by Maimonides and Thomas Aquinas regarding Jewish and Christian theology. No Moslem or Oriental scholar has attained as high a position and as strong and lasting an influence in the West as Avicenna, who has been called "the second teacher after Aristotle."[10]

A man as admired and respected as Avicenna excited jealousies and many enemies who declared that his medicines could not save his body any more than his metaphysics could save his soul. He was bitterly attacked as a sorcerer, atheist and mystic ridiculing life, to which Avicenna replied:

They cannot abide my being a physician of merit, it is painful for them to see my merits beside their ignorance. They believe they can hurt me with their slander and calumny, but their slanders and calumnies remind me of a goat who strikes the mountains with his horns.[10-12]

Avicenna's student and biographer, Juzjāni, wrote, "the Master was vigorous in all his faculties, the sexual faculty being the most vigorous and dominant of his concupiscent faculties and he exercised it often. It affected his constitution, upon whose strength he depended." During his final illness he was actively treated by his doctors and poisoned by his servants. Impatient to re-

cover, he over-treated himself, dying in service to the Amir during a military campaign at 58 years of age.

A brilliant and troubled man, Avicenna links ancient physicians with modern medicine. His devotion to the search for truth set the standard for all times. The cultures of both East and West are indebted to this great physician and philosopher, to whom we pay tribute on the 1,000th anniversary of his birth.

Up from Earth's Center through the Seventh Gate
I rose, and on the throne of Saturn sate,
And many a knot unravelled by the road,
But not the Master-knot of Human Fate.

—*The Rubaiyat of Omar Khayyám*[5]

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in memoriam

California Medical Association

Applegate, David C., Fair Oaks. Died July 18, 1980 of lymphocytic lymphoma, aged 53. Graduate of the George Washington University School of Medicine, Washington, DC, 1954. Licensed in California in 1955. Dr. Applegate was a member of the Sacramento-El Dorado Society.

Barry, John P., Blythe. Died July 24, 1980, aged 55. Graduate of the University of Pittsburgh School of Medicine, 1951. Licensed in California in 1952. Dr. Barry was a member of the Riverside County Medical Association.

Bock, Gustavus D., Long Beach. Died June 27, 1980, aged 67. Graduate of the George Washington University School of Medicine, Washington, DC, 1940. Licensed in California in 1941. Dr. Bock was a member of the Los Angeles County Medical Association.

Ducker, Bob Keith, Pacific Beach. Died August 9, 1980, aged 49. Graduate of the University of Cincinnati College of Medicine, 1957. Licensed in California in 1959. Dr. Ducker was a member of the San Diego County Medical Society.

Fullenlove, Thomas M., San Francisco. Died August 8, 1980 in San Francisco, aged 70. Graduate of the University of Louisville School of Medicine, 1934. Licensed in California in 1938. Dr. Fullenlove was a member of the San Francisco Medical Society.

Gerisch, Hans Herbert, San Pedro. Died August 10, 1980, aged 87. Graduate of Universität Leipzig Medizinische Fakultät, Saxony, 1924. Licensed in California in 1925. Dr. Gerisch was a member of the Los Angeles County Medical Association.

King, Don R., Hemet. Died July 29, 1980 in Hemet, aged 62. Graduate of the University of Illinois College of Medicine, Chicago, 1942. Licensed in California in 1942. Dr. King was a member of the Riverside County Medical Association.

Marriott, Joseph L., Alameda. Died July 23, 1980 in Walnut Creek, aged 76. Graduate of the University of Louisville School of Medicine, 1930. Licensed in California in 1932. Dr. Marriott was a retired member of the Alameda-Contra Costa Medical Association.

Matthews, Norman E. W., Paradise. Died May 19, 1979, aged 77. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1939. Licensed in California in 1939. Dr. Matthews was a retired member of the Butte-Glenn Medical Society.

McDaniel, Jack L., Concord. Died August 15, 1980, aged 42. Graduate of Louisiana State University School of Medicine, New Orleans, 1963. Licensed in California in 1968. Dr. McDaniel was a member of the Alameda-Contra Costa Medical Association.

McKenzie, Roger Bain, San Francisco. Died in 1980, aged 84. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco. 1924. Licensed in California in 1924. Dr. McKenzie was a retired member of the San Francisco Medical Society.

Mountjoy, Philip S., San Diego. Died August 5, 1980, aged 70. Graduate of Washington University School of Medicine, St. Louis, 1937. Licensed in California in 1948. Dr. Mountjoy was a member of the San Diego County Medical Society.

O'Sullivan, Martin J., Visalia. Died December 7, 1979, aged 33. Graduate of the University of Illinois College of Medicine, Chicago, 1972. Licensed in California in 1978. Dr. O'Sullivan was a member of the Tulare County Medical Society.

Richards, George H., San Francisco. Died July 5, 1980, aged 65. Graduate of the Creighton University School of Medicine, Omaha, 1941. Licensed in California in 1942. Dr. Richards was a member of the San Francisco Medical Society.

Rodman, Ronald H., Anaheim. Died May 2, 1980, aged 48. Graduate of the Chicago Medical School, 1957. Licensed in California in 1960. Dr. Rodman was a member of the Orange County Medical Association.

Ross, Verne R., Stockton. Died September 8, 1979, aged 76. Graduate of Washington University School of Medicine, St. Louis, 1928. Licensed in California in 1929. Dr. Ross was a retired member of the San Joaquin County Medical Society.

Rover, Henry P., Newport Beach. Died June 30, 1980, aged 79. Graduate of Washington University School of Medicine, St. Louis, 1926. Licensed in California in 1927. Dr. Rover was an associate member of the Los Angeles County Medical Association.

Stonier, D. Duane, Los Angeles. Died October 8, 1979, aged 85. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1924. Licensed in California in 1924. MD degree from California College of Medicine, 1962. Dr. Stonier was a retired member of the Los Angeles County Medical Association.

Tirico, Joseph G., Orange. Died August 12, 1980, aged 71. Graduate of the Royal University of Naples, Facoltà de Medicina e Chirurgia, 1933. Licensed in California in 1944. Dr. Tirico was a member of the Orange County Medical Association.

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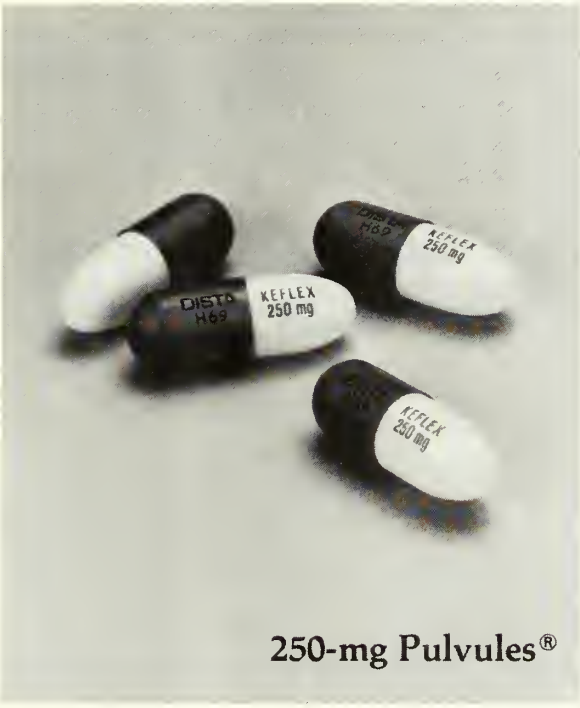

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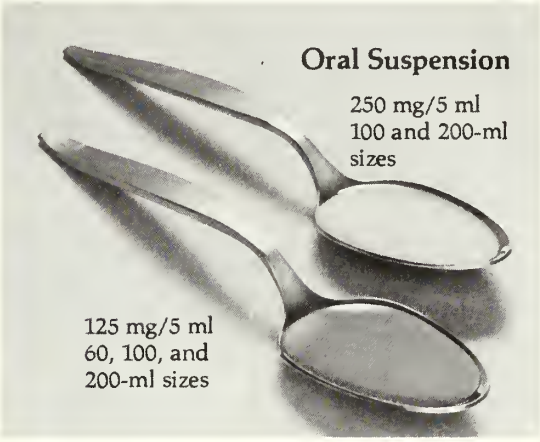

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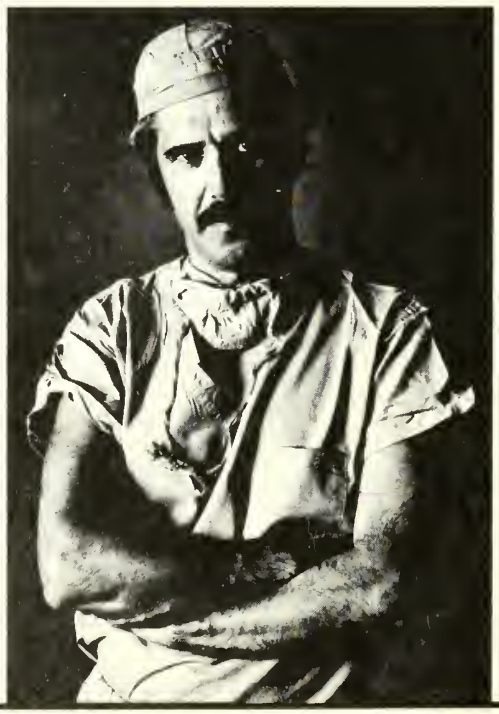

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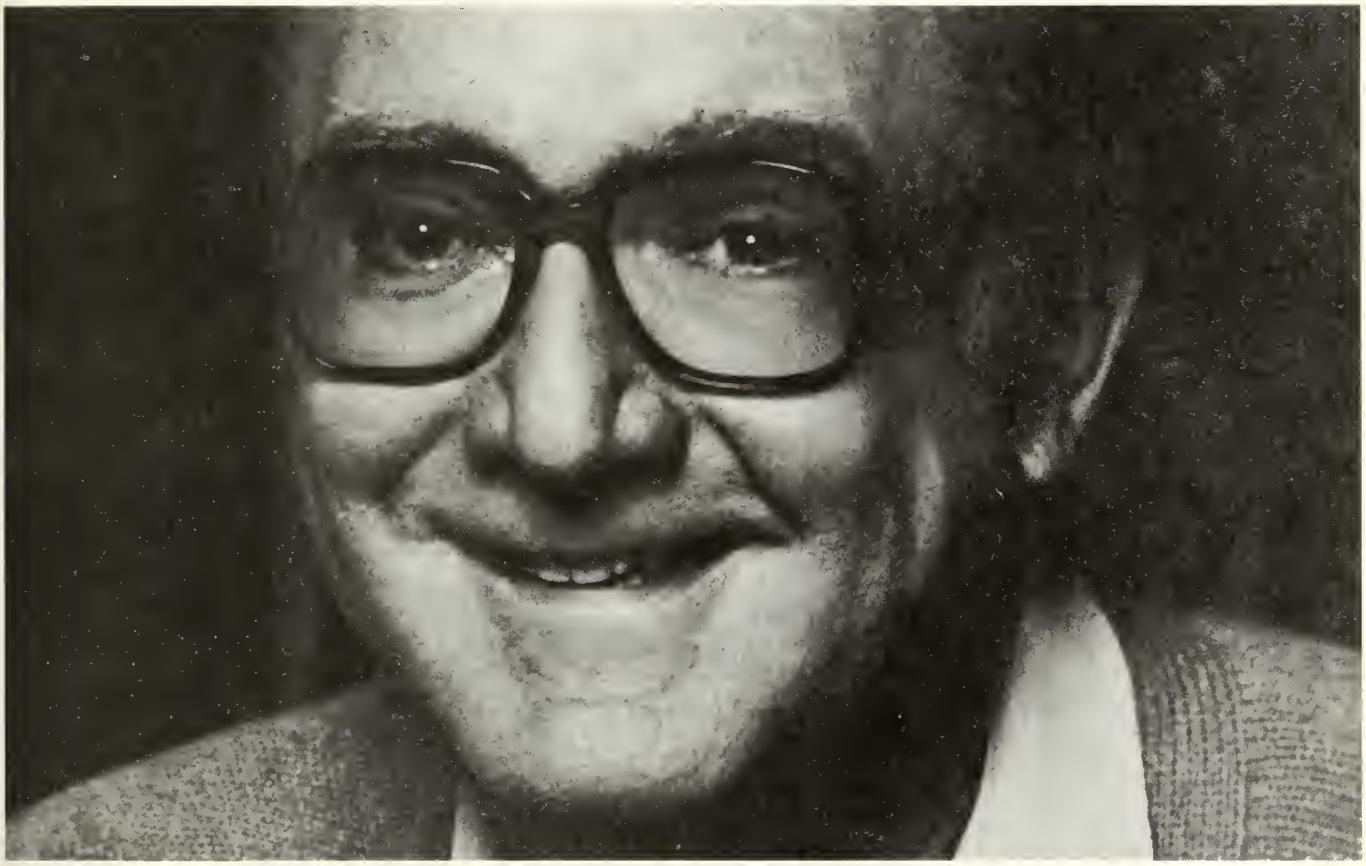

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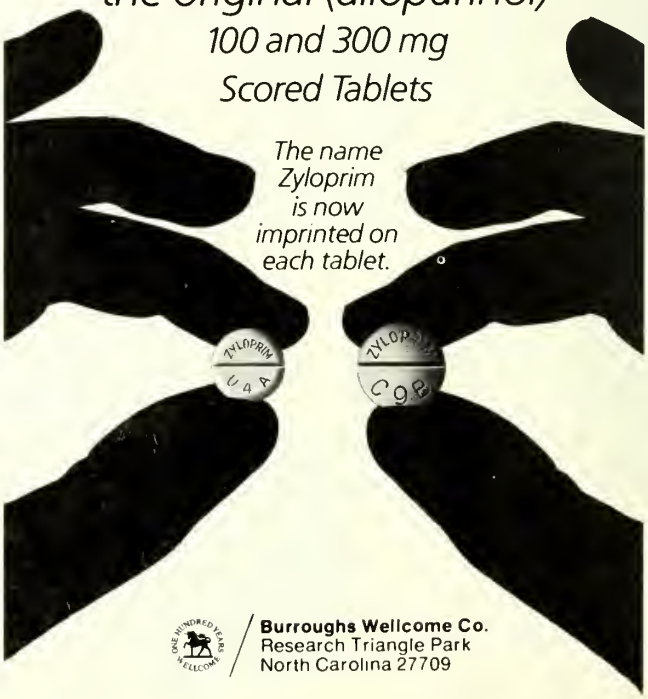

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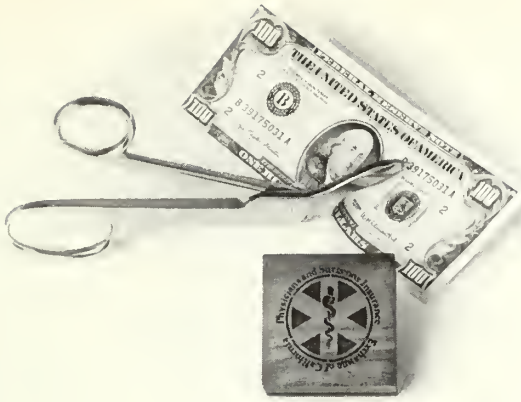

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

STRUCTURE AND FUNCTION OF THE CIRCULATION—Volume 1—Edited by Colin J. Schwartz, MD, Professor of Pathology, University of Texas Health Science Center, and Member of Scientific Staff Southwest Foundation for Research & Education, San Antonio; Nicholas T. Werthessen, PhD, Bioscientist, Office of Naval Research, Boston, and Senior Research Associate, Brown University, and Stewart Wolf, MD, Vice President, Medical Affairs, St. Luke's Hospital, Bethlehem, PA, and Professor of Medicine, Temple University, Philadelphia, and Director, Totts Gap Institute, Bangor, PA. Plenum Press, 227 West 17th St., New York City (10011), 1980. 819 pages, $75.00.

TOXICOLOGICAL AND PATHOLOGICAL STUDIES ON PSYCHOACTIVE DRUG-INVOLVED DEATHS—Louis A. Gottschalk, MD, Professor of Psychiatry and Scientific Co-Director, National Alcoholism Research Center, Department of Psychiatry and Human Behavior, College of Medicine, University of California, Irvine; and Robert H. Cravey, Chief Forensic Toxicologist, Office of the Sheriff-Coroner, County of Orange, Santa Ana, California. Biomedical Publications, P.O. Box 495, Davis, CA (95616), 1980. 472 pages, $42.00.

TRAVELING HEALTHY—A Complete Guide to Medical Services in 23 Countries—Sheilah M. Hillman, free-lance writer, and Robert S. Hillman, MD, Professor of Medicine, Director, Health Sciences Learning Resources Center, University of Washington School of Medicine, Seattle. Penguin Books, 625 Madison Avenue, New York City (10022), 1980. 538 pages, $7.95 (paperback).

ANNUAL RESEARCH REVIEWS: ANTIDIURETIC HORMONE—Volume 4—Mary L. Forsling, Middlesex Hospital Medical School, England. Pergamon Press, Inc., Maxwell House, Fairview Park, Elmsford, NY (10523), 1979. 165 pages, $26.00.

ANNUAL RESEARCH REVIEWS: ORAL CONTRACEPTIVES—Volume 4—Michael H. Briggs, Professor of Human Biology, Deakin University, Victoria, Australia; and Maxine Briggs, the Geelong Hospital, Geelong, Australia. Pergamon Press, Inc., Maxwell House, Fairview Park, Elmsford, NY (10523), 1980. 230 pages, $30.00.

ANNUAL RESEARCH REVIEWS: RENIN—Volume 4—Suzanne Oparil, Richard Katholi and Sherry Winternitz, Department of Medicine, University of Alabama Medical Center, Birmingham. Pergamon Press, Inc., Maxwell House, Fairview Park, Elmsford, NY (10523), 1979. 279 pages, $32.00.

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ANNUAL RESEARCH REVIEWS—SOMATOSTATIN—Volume 2—Mary T. McQuillan, The Russell Grimwade School of Biochemistry, University of Melbourne, Australia. Pergamon Press, Inc., Maxwell House, Fairview Park, Elmsford, NY (10523), 1980. 238 pages, $30.00.

ANNUAL RESEARCH REVIEWS: SUBSTANCE P—Volume 2—Petr Skrabanek and David Powell, Endocrine Department, Mater Misercordia Hospital, Ireland. Pergamon Press, Inc., Maxwell House, Fairview Park, Elmsford, NY (10523), 1980. 175 pages, $26.00.

BASIC BIOCHEMISTRY—Fourth Edition—Max E. Rafelson, Jr., PhD, Professor of Biochemistry, Rush Medical College; Professor of Biochemistry, Rush College of Health Sciences, Chicago; James A. Hayashi, PhD, Professor of Biochemistry, Rush Medical College; Professor of Biochemistry, Rush College of Health Sciences; and Anatoly Bezkorovainy, PhD, Professor of Biochemistry, Rush Medical College; Professor of Biochemistry, Rush College of Health Sciences. Macmillan Publishing Co., Inc., 866 Third Ave., New York City (10022), 1980. 418 pages, $14.95.

BASIC HISTOLOGY—Third Edition—Luis C. Junqueira, MD, Professor of Histology & Embryology, Institute of Biomedical Science, University of Sao Paulo, Brazil, Honorary Research Associate in Biology, Harvard College, Boston; and José Carneiro, MD, Professor of Histology & Embryology, Institute of Biomedical Science, University of Sao Paulo, Brazil, Formerly Research Associate, Department of Anatomy, Medical School, McGill University, Montreal. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 504 pages, $15.50.

BEHAVIORAL DISORDERS: Understanding Clinical Psychopathology—Igor Grant, MD, University of California, San Diego, School of Medicine. SP Medical & Scientific Books—Division of Spectrum Publications, Inc., 175-20 Wexford Terrace, Jamaica, NY (11432), 1979, 316 pages.

CESAREAN CHILDBIRTH—A Handbook For Parents—Christine Coleman Wilson and Wendy Roe Hovey. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1980. 297 pages, $6.95 (paperback).

CONTINUING MEDICAL EDUCATORS' HANDBOOK—A joint project of Colorado Medical Society, University of Colorado Health Sciences Center, Colorado Foundation for Medical Care—Edited by Kevin P. Bunnell, EdD, Executive Director, Colorado Consortium for Continuing Medical Education. CCCME—Kevin Bunnell, EdD, Director, 1601 E. 19th Avenue, Denver, CO (80218), 1980. 68 pages, $9.00 (orders of 5 or more copies available at a 10 percent discount).

DRUG AND CHEMICAL RISKS TO THE FETUS AND NEWBORN—Volume 36 in the series: PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH—Editors: Richard H. Schwarz, MD, Professor and Chairman, Department of Obstetrics/Gynecology, State University of New York, Downstate Medical Center, Brooklyn; and Sumner J. Yaffe, MD, University of Pennsylvania School of Medicine; Director, Division of Clinical Pharmacology, Children's Hospital, Philadelphia, Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1980. 166 pages, $20.00.

EMERGENCY HANDBOOK—A First Aid Manual for Home and Travel—Peter Arnold; with Edward L. Pendagast, Jr., MD, Consulting Physician. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1980. 250 pages, $11.95.

HOME CARE: A Practical Alternative to Extended Hospitalization—Evelyn M. Baulch. Celestial Arts, 231 Adrian Road, Millbrae, CA (94030), 1980. 256 pages, $12.95 (cloth), $8.95 (paperback).

INADVERTENT MODIFICATION OF THE IMMUNE RESPONSE—The Effects of Foods, Drugs, and Environmental Contaminants—Proceedings of the Fourth FDA Science Symposium—Edited by I. M. Asher, PhD, FDA, Office of Health Affairs. US Dept of Health and Human Services, Public Health Service, FDA, HHS Publication No. (FDA) 80-1074. Available from Dr. Irvin M. Asher, HFY-313, FDA Scientific Liaison Staff, Rockville, MD (20857) 319 pages, Fee: NONE (limited to initial printing).

THE OSTOMY BOOK—Living Comfortably With Colostomies, Ileostomies, and Urostomies—Barbara Dorr Mullen and Kerry Anne McGinn, RN, Bull Publishing Company, P.O. Box 208, Palo Alto, CA (94302), 1980. 236 pages, $7.95 (paperback).

PRACTICAL ONCOLOGY—Edited by Gregory Sarna, MD, Director, Bowyer Multidisciplinary Clinic; Assistant Professor of Medicine, Division of Hematology/Oncology, Department of Medicine, UCLA School of Medicine, Los Angeles—in the series POSTGRADUATE MEDICINE FOR THE PRIMARY CARE PHYSICIAN—Series Editors-in Chief: Sherman Mellinkoff, MD, and David H. Solomon, MD. Houghton Mifflin Professional Publishers, Medical Division, Two Park St., Boston (02107), 1980. 223 pages, $18.00.

PRACTICE OF GERIATRIC PSYCHIATRY—Alex Comfort, MB, BCh, DSc, Consultant, Geriatric Psychiatry, Brentwood Veterans Administration Medical Center, Los Angeles, and formerly Head, Medical Research Council, Research Group on Aging, University College, London. Elsevier North Holland, Inc., 52 Vanderbilt Ave., New York City (10017), 1980. 110 pages, $15.95.

THE PSYCHOLOGICAL WAY/THE SPIRITUAL WAY—Martin Bobgan, EdD, and Deidre Bobgan, MA, Co-directors of Counseling Ministry, Living Faith Center, Santa Barbara, California. Bethany Fellowship, Inc., 6820 Auto Club Road, Minneapolis, MN (55438), 1979. 219 pages, $5.95 (paperback).

WATER FIT TO DRINK—A Guide to the Hidden Hazards of Drinking Water and What You Can Do To Ensure a Safe, Good-Tasting Supply for the Home—Carol Keough. Rodale Press, Inc., Emmaus, PA (18049), 1980. 265 pages, $8.95.

WHOLE AGAIN—Lee Whipple. Caroline House Publishers, Inc., P.O. Box 738, Ottawa, IL (61350), 1980. 232 pages, $9.95.

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ANESTHESIOLOGY

November 8-9—**American Society of Anesthesiologists—Refresher Course.** Hilton, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

December 12-14—**Anesthesia: Before and After.** Tucson Hospitals Medical Education Program at Canyon Hotel, Palm Springs. Friday-Sunday. $150. Contact: James P. Angiulo, MD, Kino Community Hosp., 2800 E. Ajo Way, Tucson, AZ 85713.

January 6-10—**Anesthesia Update.** UCSD at Hotel del Coronado, Coronado. Tuesday-Saturday. 20 hrs. $250.

January 23-25—**Pediatric Anesthesiology—19th Clinical Conference.** Childrens Hospital of Los Angeles at Marriott Hotel, Los Angeles. 15 hrs. $165. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 14-21—**9th Obstetric Anesthesia Conference.** Ohio State Univ. at Sheraton Waikiki, Honolulu. One week. 25 hrs. Contact: Excursions Unlimited, Inc., c/o OSU Dept. of Anesthesiology, 1820 Northwest Blvd., Columbus, OH 43212. (800) 848-4438.

CANCER

October 24-26—**Cancer and Enzymes.** UCSD at Vacation Village, San Diego. Friday-Sunday.

October 27-29—**4th Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. 22 hrs. $300. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

November 6-8—**Current Concepts in Cancer Diagnosis.** UCLA. Thursday-Saturday.

November 7-8—**Cancer Prevention and Screening.** Claire Zellerbach Saroni Tumor Institute of Mt. Zion Hospital and Medical Center at Holiday Inn on Union Square, San Francisco. Friday-Saturday. 10 hrs. $125 before September 15; $150 thereafter. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

November 15—**Current Advances in Cancer Care.** Eden Hospital and American Cancer Society, Alameda Chapter, at Hilton Hotel, Oakland. Saturday. Contact: Joseph C. Beck, MD, Dept. of Radiology, Eden Hosp., 20103 Lake Chabot Rd., Castro Valley 94546. (415) 537-1234, ext. 252.

November 21—**Modern Management of Anorectal Carcinoma.** USC Cancer Center and American Cancer Society at Bonaventure Hotel, Los Angeles. Friday. Contact: Robert J. McKenna, MD, Dir., USC Comprehensive Cancer Ctr., 1721 Griffin Ave., Los Angeles 90031. (213) 226-4041.

January 22-24—**Current Concepts in Cancer Diagnosis.** UCLA at Century Plaza Hotel, Los Angeles. Thursday-Saturday.

January 23-24—**Cancer Update 1981.** Peralta Hospital at Goodman's Hall, Jack London Square, Oakland. Friday-Saturday. 10 hrs. Contact: Susan Ford, Education and Training Dept., Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 2327.

January 24-25—**Current Approaches to Radiation Oncology.** UCSF at Sir Francis Drake Hotel, San Francisco. Saturday-Sunday.

January 30-February 1—**Midwinter Oncology Conference—for Radiation Oncologists.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $150. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

February 12-13—**Controversies in Lung Cancer.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 14 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** See Medicine, February 23-26.

February 25—**Ovarian Cancer.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
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UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

February 28-March 1—**Recent Advances in Cancer Diagnosis.** UCLA. Saturday-Sunday.

EMERGENCY MEDICINE

October 16—**Dermatology in the Emergency Department.** UCSD. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

October 20-31—**Intensive Review of Emergency Medicine.** USC. Two weeks.

October 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

November 3-5—**Postgraduate Institute for Emergency Physicians, Symposium IV.** UCSD at Hilton, San Diego. Monday-Wednesday.

November 20—**Clinical Pharmacology in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

December 8-12—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

December 10—**Emergency Medicine.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

January 15-20—**Emergency Medicine.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Tuesday.

January 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

January 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

February 16-20—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

March 23-27—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

MEDICINE

October 15-16—**Advanced Electrocardiography.** St. Francis Medical Center, Lynwood. Wednesday-Thursday. 12 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

October 18-19—**Current Concepts in Cardiology and Hypertension.** Kaiser Foundation Hospital at Red Lion Inn, Sacramento. Saturday-Sunday. 8 hrs. $10. Contact: Cheryl English, Med. Ed. Office, Kaiser Fndn. Hosp., 2025 Morse Ave., Sacramento 95825. (916) 486-5965.

October 18-25—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $325.

October 23-28—**Pacific Dermatologic Association.** Hilton Riviera, Palm Springs. Thursday-Tuesday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno, NV 89509. (702) 323-2461.

October 27-30—**Practical Electrocardiography Course for Primary Physicians.** Memorial Hospital Medical Center-UCI Center for Health Education at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 29—**Endocrine Review.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Dept. of Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

October 30-November 1—**Cardiology Update 1980.** American College of Cardiology at Del Monte Hyatt, Monterey. Thursday-Saturday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 30-November 2—**California Society of Internal Medicine—Annual Meeting.** Doubletree Inn, Monterey. Thursday-Sunday. Contact: Carol Parlette, Exec. Dir., CSIM, 703 Market St., 1412 Central Tower, San Francisco 94103. (415) 362-1548.

November 1—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75.

November 5-8—**American Thyroid Association.** Holiday Inn at the Embarcadero, San Diego. Wednesday-Saturday. Contact: Dorothy Hickler, Exec. Sec., ATA, Univ. of MA Medical Ctr., 55 Lake Ave. N., Worcester, MA 01605. (617) 856-3115.

November 8—**Second Annual Winter Symposium on Cardiology.** Bay General Community Hospital at Hotel del Coronado, Coronado. Saturday. 10 hrs. $65. Contact: Medical Staff Office, Bay Gen. Community Hosp., 435 H St., Chula Vista 92010. (714) 420-8182, ext. 233 or 241.

November 12—**Peptic Ulcer—Its Diagnosis and Treatment in the 1980's.** LLU. Wednesday. 4 hrs. $30.

November 13-15—**Allergy/Immunology for the Practicing Physician.** UCSF. Thursday-Saturday. 18 hrs. $180.

November 17-19—**International Symposium on Status Epilepticus.** UCLA at Miramar-Sheraton, Santa Monica. Monday-Wednesday. 20 hrs.

November 21-22—**Advances in the Diagnosis and Management of Liver Disease.** Huntington Memorial Hospital at Huntington Sheraton Hotel, Pasadena. Friday-Saturday. 8 hrs. Contact: Mrs. Arlene M. Ellis, Coordinator, Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105. (213) 440-5165.

November 29-December 1—**Advances in Heart Disease 1981.** American College of Cardiology at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 1-3—**Cardiovascular-Pulmonary Update for the Practicing Physician.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 19 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

December 5—**Recognition and Management of Bleeding Disorders.** Children's Hospital Medical Center of Northern Calif. at Sir Francis Drake Hotel, San Francisco. Friday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

December 5-7—**Cardiac Rehabilitation.** International Medical Education Corp. at Wilshire Hyatt, Los Angeles. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

December 5-7—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Desert Inn, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

December 6—**Diagnosis and Treatment of Venous Thromboembolism.** PMC. Saturday.

December 6-7—**Neurology for the Primary Care Physician.** UCLA. Saturday-Sunday.

December 10—**Collagen Disease—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $30.

December 11-14—**Intensive Care for Neurological Trauma and Disease: A New Decade.** Comprehensive Central Nervous System Injury Foundation and Univ. of Miami at Vacation Village, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Comprehensive CNS Injury Fndn., P.O. Box 9494, San Diego 92109.

December 13—**Endocrinology and Metabolism in the 80's: A New Frontier.** Daniel Freeman Hospital Medical Center at Hyatt House, Los Angeles. Saturday. 6 hrs. $100. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp. Med. Ctr., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 3427.

December 14-20—**Immunohematology: New Concepts in Clinical Application.** Univ. of Pennsylvania School of Medicine and International Center for Health Education at Kauai Surf Hotel, Kauai, Hawaii. One week. Contact: Internat'l Health Resource Ctr. of Hawaii, P.O. Box 3109, Lihue, Kauai, Hawaii 96766. (808) 245-2121.

January 9-11—**Debates, Controversies and Concepts in the Treatment of the High Risk Patient.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Friday-Sunday. 19 hrs. $225. Contact: Lore Kahane, Rm. 2049, Cedars-Sinai Med. Ctr., P.O. Box 48750, Los Angeles 90048. (213) 855-5547.

January 10-11—**Practical Pulmonary Diseases.** UCLA. Saturday-Sunday.

January 14—**Arrhythmias—Their Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $30.

January 24—**Cardiology Seminar—10th Annual.** Fresno Community Hospital and Medical Center. Saturday. Contact: Joann Ellis, Ed. and Training Dept., Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

January 26-28—**Practical Management of Bronchial Asthma and Asthmatic Bronchitis.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

January 30-31—**Cardiology Update — 1981 — The Changing Scene.** St. Francis Medical Center at Bonaventure Hotel, Los Angeles. Friday-Saturday. 14 hrs. Contact: Allan Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603- 6174.

February 2-4—**Clinical Echocardiography—1981.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 4—**Endocrine Disorders.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

February 4-6—**Children With Heart Disease.** USC at Gene Autry Hotel, Palm Springs. Wednesday-Friday. 14 hrs.

February 4-6—**Western Section of the Society for Investigative Dermatology, Western Section of American Federation for Clinical Research, Western Society for Clinical Research.** Carmel. Wednesday-Friday. Contact: Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, NJ 08086.

February 11-13—**Recent Advances in Neurology.** UCSF. Wednesday-Friday.

February 14—**Sixth Annual Liver Conference: Cirrhosis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 14-15, 21-22—**Dermatology.** UCLA. Two weekends.

February 16-18—**Recent Advances in Clinical Endocrinology.** UCSF at Sir Francis Drake Hotel, San Francisco. Monday-Wednesday.

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February 18-20—**Neuro-Orthopedic Screening.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 18-April 22—**Gastroenterology.** UCLA. Wednesday evenings.

February 19-21—**Immunology.** STAN. Thursday-Saturday. 13 hrs. $245.

February 19-21—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Fndn., American Heart Assn., American Lung Assn., Nat'l Critical Care Institute of Education, Vascular Disease Fndn. at Mission Bay Hilton, San Diego. Thursday-Saturday. $250. Contact: CREF, P.O. Box 33185, San Diego 92103.

February 21-28—**Metabolism and Endocrinology.** Univ. of Washington School of Medicine at Kona Surf Hotel, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 21-28—**Practical Neurology.** Univ. of Washington School of Medicine at Ilikai Hotel, Honolulu. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** Scripps Clinic and Research Fndn. at Vacation Village, San Diego. Monday-Thursday. 25 hrs. $290. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 25—**Hospital Acquired Infections.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 2-4—**Neuroscience for Neurologists and Psychiatrists.** STAN. Monday-Wednesday. 13 hrs. $240.

March 2-4—**Dermatology for Internists.** STAN at Eisenhower Medical Center, Rancho Mirage. Monday-Wednesday.

March 4-7—**Immunology and Clinical Practice of Allergy—5th Annual Course.** UCSD at Hilton, San Diego. Thursday-Saturday. 20 hrs.

March 6—**8th Annual Diabetes Program.** UCD at Red Lion Motor Inn, Sacramento. Friday. 6½ hrs.

March 8-11—**Consultants' Course in Dermatology.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

March 15-19—**American College of Cardiology.** San Francisco. Sunday-Thursday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 15-20—**Symposium on Gastroenterology.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Friday.

March 23-April 4—**Intensive Review of Internal Medicine—29th Annual.** USC. Two weeks.

OBSTETRICS AND GYNECOLOGY

November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** UCSD at Bahia Hotel, San Diego. Wednesday-Friday. 19 hrs. $185. Contact: Ronald W. Coen, MD, UCSD Sch. of Med., C-019, La Jolla 92093. (714) 452-4424.

December 5-7—**5th Annual Symposium on Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort. Friday-Sunday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 10-17—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

January 14-17—**Postgraduate Course on Basic and Advanced Gyn Urology: Theory and Practice.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Wednesday-Saturday. 20 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 25-30—**Obstetrics-Gynecology Update: 1981.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

January 26-30—**10th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday. 36 hrs. $400.

February 7-8—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. Contact: Dee Davis, Exec. Sec., LAOGS, 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

PEDIATRICS

October 15—**Pediatric Urology.** See Surgery, October 15.

October 25—**Hearing Impaired Child.** Peninsula Hospital, Burlingame. Saturday. Contact: Susan Norrell, c/o Radiology Dept., Peninsula Hosp., 1783 El Camino Real, Burlingame 94010. (415) 697-4061, ext. 479.

October 25-November 1—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education and L.A. Pediatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $200. Contact: Center for Health Education, MHMC, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 27-31—**4th Annual Pediatrics for the Practitioner—A Pediatric Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday. 21 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 1—**Pediatric Dermatology Seminar.** See Medicine, November 1.

November 5-7—**Tomorrow: A Follow-Up on Perinatal Care.** See Obstetrics-Gynecology, November 5-7.

November 15—**Pediatric Ophthalmology for the Primary Care Physician.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 4 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

November 21-24—**Pediatric Update.** American Academy of Pediatrics, Calif. Chapters 1, 2 and 3, at Hilton Hotel, Las Vegas. Friday-Monday. 15 hrs. $175, members; $200, nonmembers. Contact: AAP, Chap. 2, P. O. Box 2134, Inglewood 90305.

December 3-7—**5th Annual Pediatric Seminar.** Los Angeles Pediatric Society at Kahala Hilton, Honolulu. Wednesday-Sunday. 11 hrs. $75. Contact: Los Angeles Pediatric Soc., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

December 5-7—**Children and Their Skeletons: A Practical Approach.** UCD at Hyatt Del Monte, Monterey. Friday-Sunday.

February 4-6—**Children With Heart Disease.** See Medicine, February 4-6.

PSYCHIATRY

October-January—**Mental Research Institute Workshops.** Palo Alto. Series of workshops on Brief Therapy; Hypnotherapy; The Interactional Approach: Conceptual Explorations; Family Therapy; The Interactional Approach in Medical and Dental Practice. Contact: Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 24-26—**Contemporary Psychotherapies.** Southern California Psychiatric Society at Doubletree Inn, Monterey. Friday-Sunday. 7 hrs. Contact: SCPS, 9744 Wilshire Blvd., Beverly Hills 90212. (213) 271-7219.

October 25—**Cognitive Prospectives in Psychiatry.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 14-16—**Infant Psychiatry III: Pathological Infants and Their Parents; Pathological Parents and Their Infants.** UCSF. Friday-Sunday.

November 17-21—**Group Therapy.** UCSF. Monday-Friday.

November 22—**Family Interventions as an Alternative to Psy-**

chiatric Hospitalization. Mental Research Institute, Palo Alto. Saturday. 7 hrs. $50. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 23-30—**New Directions in Psychiatry.** Univ. of Washington School of Medicine at Ilikai Hotel, Honolulu. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

January 14-May 27—**Practicum on Family Therapy and Schizophrenia.** Mental Research Institute, Palo Alto. Wednesdays. 80 hrs. $600. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 25-31—**7th Annual Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. One week. 26 hrs.

January 30-31—**Heinz von Foerster on Cybernetics, Language, and Understanding.** Mental Research Institute, Palo Alto. Friday-Saturday. 12 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

March 2-4—**Neuroscience for Neurologists and Psychiatrists.** See Medicine, March 2-4.

RADIOLOGY AND PATHOLOGY

October 24-26—**Advances in Immunopathology.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Friday-Sunday. 17 hrs. $120. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

October 28-30—**Gram Negative Organisms: An Approach to Identification.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Thursday. 21 hrs. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

November 1—**Radiology for Clinicians—1980.** Cedars-Sinai Medical Center at Century Plaza, Los Angeles. Saturday. 7 hrs. $80. Contact: Lore Kahane, Rm. 2049, Cedars-Sinai Med. Ctr., P.O. Box 48750, Los Angeles 90048. (213) 855-5547.

December 13-14—**Using the Clinical Lab.** UCLA. Saturday-Sunday.

January 19-23—**Interventional Radiologic Techniques: Computed Tomography and Ultrasonography.** UCSF at Fairmont, San Francisco. Monday-Friday. $350.

January 19-24—**Review Course in Clinical Ob, Gyn, and Histological Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Monday-Saturday. 41 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 21-23—**8th Annual Postgraduate Course in Genitourinary Pathology**. Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 22½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 24-31—**International Diagnostic Radiology Conference.** UCSF at Maui Surf Hotel, Maui, Hawaii. One week.

January 30-February 1—**33rd Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $150. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

February 4-6—**Recent Progress in Diagnostic Laboratory Immunology.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 24 hrs. $250. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 9-12—**Molecular Basis of Cell-Cell Interaction.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Monday-Thursday. 24 hrs. $165. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 11—**Neuroradiology—Its Use, Indications and Values in Strokes, Tumors and Head Trauma.** LLU. Wednesday. 4 hrs. $30.

February 18-20—**Anaerobic Bacteriology Methods.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 15 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27-March 1—**Neuroradiology.** USC. Friday-Sunday. 20 hrs. $200.

March 4-7—**Sierra Radiology Conference—2nd Annual.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at North Lake Tahoe. Wednesday-Saturday. 18 hrs. $245. Contact: Michael H. Reid, PhD, MD, Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

March 6-8—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Friday-Sunday.

March 9-13—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $350.

March 13-19—**College of American Pathologists/American Society of Clinical Pathologists—Joint Spring Meeting.** Town and Country, San Diego. Friday-Thursday. Contact: Joan Lipe, CAP, 7400 N. Skokie Blvd., Skokie, IL 60077. (312) 677-3500.

March 14-15—**B-Scan Ultrasonography: Update.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

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SURGERY

October 15—**Pediatric Urology—8th Annual Postgraduate Conference.** Los Angeles Urological Society at Marriott Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Trudy Mackel, LAUS, P.O. Box 836, Lomita 90717. (213) 326-7418.

October 24-25—**Cataract Surgery and Intraocular Lenses Course: Planned Extracapsular, Phacoemulsification and Intracapsular Techniques.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $350. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

October 25-November 1—**Operative Arthroscopy.** UCLA at Maui, Hawaii. One week.

November 6-8—**Sterling Bunnell Memorial Lectureship.** UCSF, Dept. of Orthopaedic Surgery. Thursday-Saturday. 18 hrs. $200.

November 6-9—**International College of Surgeons, United States Section—Annual Meeting.** Aladdin Hotel, Las Vegas. Thursday-Sunday. Contact: Mr. Pat Quinn, Admin. Dir., ICS, 1516 N. Lake Shore Dr., Chicago 60610.

November 7-8—**Leg Amputations and Their Rehabilitation.** PMC at Hyatt on Union Square, San Francisco. Friday-Saturday. 12 hrs. $185.

November 14-15—**Vitrectomy/Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs. $450.

December 3-4—**6th Annual Meeting and Scientific Symposium —Lyman A. Brewer, III, International Surgical Society—Controversies in the Management of Coronary Heart Disease.** White Memorial Medical Center at Hilton, Los Angeles. Wednesday-Thursday. Contact: Dr. Howard Whigham, Dir., Research and CME, White Mem. Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 263-6100.

December 6—**Practical Workshop on Surgery of the Eyelids, Lacrimal System and Orbit.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $275. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

December 11-13—**Trauma.** No. Calif. Chap of the Committee on Trauma of Am. College of Surgeons at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. Contact: Donald D. Trunkey, MD, Chief of Surgery, S.F. Gen. Hosp., 1001 Potrero Ave., San Francisco 94110.

December 11-14—**Intensive Care for Neurological Trauma and Disease: A New Decade.** See Medicine, December 11-14.

December 12-13—**Ophthalmology Update.** UCD, UCSF, PMC, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

January 9-11—**Debates, Controversies and Concepts in the Treatment of the High Risk Patient.** See Medicine, January 9-11.

January 10—**Photocoagulation Therapy.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

January 23-24—**Third Annual Postgraduate Course in Surgery.** UCD at Point West Hotel, Sacramento. Friday-Saturday. 14 hrs. $85.

January 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

January 25-30—**Assembly in Surgery—4th Annual.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sunday-Friday. 28 hrs.

February 4-6—**Current Thinking in the Management of Ocular and Adnexal Tumors.** UCSF. Wednesday-Friday.

February 5-7—**Aesthetic Rhinoplasty and Nasal Reconstruction.** UCLA. Thursday-Saturday.

February 6-8—**National Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery and American Society for Dermatologic Surgery at Ramada Inn, Beverly Hills. Friday-Sunday. Contact: Drs. Richard Fleming, Toby Mayer, Peter Goldman, 9730 Wilshire Blvd., Ste. 216, Beverly Hills 90212.

February 8-10—**The Mandible: Surgical Treatment of Congenital and Acquired Deformities.** UCLA. Sunday-Tuesday.

February 14-20—**Neurological Surgery of the Ear and Skull Base—3rd International Workshop.** Ear Research Institute at Newporter Inn, Newport Beach. One week. 32 hrs. $500. Contact: Derald E. Brackmann, MD, Neurological Workshop, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

February 19-21—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** See Medicine, February 19-21.

February 26-March 3—**American Academy of Orthopaedic Surgeons.** Convention Center, Las Vegas. Thursday-Tuesday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

March 5-7—**Calculi.** American Urological Association at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: AUA, Office of Education, Texas Med. Ctr., 4th Fl-Inst. of Religion Bldg., 1129 Wilkins, Houston, TX 77030.

March 6-7—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 11—**Common Fractures and Joint Injuries.** LLU. Wednesday. 4 hrs. $30.

March 21-22—**ECG Course for Oral and Maxillofacial Surgeons.** UCSF. Saturday-Sunday.

March 25-28—**4th Annual U.S. IOL Symposium.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Wednesday-Saturday. Contact: Debbi Miller, Dir. of Mtg. Services, Am. Intra-Ocular Implant Soc., P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

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October 15-18—**24th Annual Western Occupational Health Conference.** Western Occupational Med. Assn. at Hotel del Coronado, Coronado. Wednesday-Saturday. Contact: Joe Donovan, WOHC, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 16-18—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 24—**Patient Care—Challenging the Image.** St. Francis Medical Center at Sheraton Hotel, Anaheim. Friday. 7 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

October 24-25—**Geriatric Medicine Today.** Western Div., Am. Geriatrics Soc., at Hyatt Regency, San Francisco. Friday-Saturday. Contact: AGS, Western Div., 13220 105th Ave., Bldg. B, Rm. 61, Sun City, AZ 85351.

October 24-26—**In Pursuit of Wellness.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

October 25-26—**Eight Common Problems.** UCLA. Saturday-Sunday.

October 28-31—**American Academy of Occupational Medicine.** Hyatt Regency, San Francisco. Tuesday-Friday. Contact: AAOM, 150 N. Wacker Dr., Chicago 60606.

October 30-November 1—**Postgraduate Institute on Nutrition.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 31-November 1—**Understanding Cross-Cultural Differences in Illness and Among Hispanic and Indochinese Immigrants/Refugees.** UCLA. Friday-Saturday. $75.

November 1—**Second Annual Medical Symposium.** El Cajon Valley Hospital at Hotel del Coronado, Coronado. Saturday. 5 hrs. $35. Contact: Ray Leber, El Cajon Valley Hosp., 1688 E. Main St., El Cajon 92021. (714) 440-1122.

November 2-5—**California Academy of Family Physicians—Annual Scientific Assembly.** Disneyland Hotel, Anaheim. Sunday-Wednesday. Contact: William W. Rogers, Exec. Sec., CAFP, 9 First St., Rm. 900, San Francisco 94105. (415) 982-6091.

November 3-7—**Postgraduate Institute for Primary Care Physicians.** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $275.

November 3-7—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $290.

November 5—**Sexuality.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Medical Center, 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

November 6-9—**Practical Hypnosis: Introductory and Intermediate Courses.** San Diego Society of Clinical Hypnosis and UCSD. Thursday-Sunday. 21 hrs. $290. Contact: UCSD.

November 8—**Psychiatry for the Primary Care Physician: Close Encounters of the Troubling Kind.** UCD at Red Lion Inn, Sacramento. Saturday. 7½ hrs. $65.

November 8-9—**Cross Cultural and Trans Cultural Issues in Family Health Care.** UCSF. Saturday-Sunday. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

November 13-15—**Medical Aspects of Products Liability.** UCSF. Thursday-Saturday.

November 13-16—**Biofeedback and Family Practice Medicine.** UCLA and Biofeedback Society of Calif. at Le Baron Hotel, San Jose. Thursday-Sunday. 15½ hrs. $175.

November 15—**Criteria for Evaluating Pseudoscience, Cults and Holistic Medicine.** San Jose State University. Saturday. 8 hrs. $40. Contact: Susan M. Grube, MPH, Cont. Ed., San Jose State Univ., Washington Sq., San Jose 95192. (408) 277-3778.

November 15-16—**Fourth Annual National Symposium on Aging.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

November 16—**Frontiers in Medicine—12th Annual Symposium.** UCLA and Granada Hills Community Hospital at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344.

November 17-18—**The Medical Consequences of Nuclear Weapons and Nuclear War.** UCSF and Physicians for Social Responsibility at War Memorial Veterans Bldg., San Francisco. Monday-Tuesday. 11 hrs. $75. Contact: Physicians for Social Responsibility, P.O. Box 144, Watertown, MA 02172. (617) 924-3568.

November 21-23—**Sports Medicine: The Physician and the Athlete.** UCD at Marriott Inn, Berkeley. Friday-Sunday. 12 hrs. $140.

November 21-25—**Gerontological Society—Annual Scientific Meeting.** Town and Country Hotel, San Diego. Friday-Tuesday. Contact: Dr. Eugene J. Towbin, VA Hospital, Little Rock, AR 72206.

December 4—**Nutrition and Aging.** STAN. Thursday. 7 hrs.

December 5-7—**Human Sexuality.** Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

December 6-7—**Second Annual Patient Education Research Seminar.** UCSF. $100. Contact: Cont. Ed. in Health Sciences, UCSF, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

December 13—**Diagnosis and Treatment of Sleep Disorders Patients.** STAN at Marriott, Santa Clara. Saturday. 7 hrs. $35.

January 9-10—**New Concepts in Management of Chronic Pain.** Bay General Community Hospital at Half Moon Inn, Shelter Island, San Diego. Friday-Saturday. 10 hrs. $45. Contact: Karen Johnson, Bay Gen. Community Hosp., 435 H St., Chula Vista 92010. (714) 420-8182.

January 17—**The Virus of Love: Genital Herpes Infection.** UCLA. Saturday.

January 19-23—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday. 25 hrs. $290.

January 23—**Diagnosis and Treatment of Sleep Disorders Patients.** STAN at Marriott, Santa Clara. Friday. 7 hrs. $35.

January 25-31—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. One week. 50 hrs. Contact: Cont. Ed. in Health Sciences, UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

February 11-13—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Wednesday-Friday. 22 hrs. $275.

February 19-22—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Thursday-Sunday. 14 hrs.

February 20-21—**Pain: New Approaches to Treatment.** Mesa Vista Hospital and Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Virginia Everett, Vista Hill Fndn., 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 23-27—**Basic Science for Clinicians.** STAN. Monday-Friday. 24 hrs. $290.

March 5-8—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Thursday-Sunday.

March 5-8—**Sports Medicine.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday.

March 13-15—**Clinical Management.** STAN at The Lodge, Pebble Beach. Friday-Sunday. 8 hrs.

March 13-18—**California Medical Association—110th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

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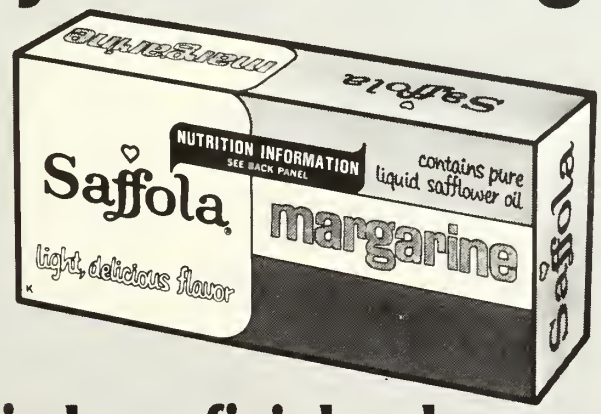

Good Housekeeping PROMISES LIMITED WARRANTY TO CONSUMERS REPLACEMENT OR REFUND IF DEFECTIVE

Higher in beneficial polyunsaturates. Contains no cholesterol. And tastes great.

Saffola is beneficial as part of a fat modified diet to help reduce serum cholesterol.

March 16-27—**Intensive Residency in Occupational Medicine, Session II.** UCSF. Two weeks.

March 18-20—**Recent Advances in Clinical Nutrition.** UCSD at Vacation Village, San Diego. Wednesday-Friday. 17 hrs.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Margaret H. Griffith, Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

October 22—**Pap Smears—Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

October 30—**Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

December 11—**Women, Violence and Sexuality—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatry Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

January 28—**Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

February 5—**Endorphins—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 19—**Right Brain Functioning—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 25—**Gardnerella Vaginalis Vaginitis—Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

April 30—**Group Therapy—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

May 27—**Univ. of Wash. Ob/Gyn Session** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

June 18—**Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

October 22-23—**Review of Selected Topics in Upper GI Disease—Univ. of Wash. Internal Medicine Review Sessions.**

October 22, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

October 23, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

October 24—**Volcano Lung—Univ. of Wash. Internal Medicine Review Sessions** (Missoula). Friday. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 58901. (406) 549-3782.

November 19—**Congenital Defects—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

November 19—**Medical Oncology—Univ. of Wash. Internal Medicine Review Sessions.**

November 19, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

November 20, Thursday, Billings. 7-9:30 a.m. Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

November 21, Friday, Missoula. 8-10:30 a.m. St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

December 10—**Endocrinology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 10-12—**Pain—Univ. of Wash. Internal Medicine Review Sessions.**

December 10, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 11, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

December 12, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

January 21-25—**Sexually Transmitted Diseases—Univ. of Wash. Internal Medicine Review Sessions.**

January 21, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

January 22, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

January 23, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 11—**Pediatric Anesthesiology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 18-20—**Adolescent Medicine—Univ. of Wash. Internal Medicine Review Sessions.**

February 18, Wednesday, Great Falls. 5-7:30 p.m. Deaconess Hospital. Contact F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 19, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

February 20, Friday, Missoula. 8-10:30 a.m. St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 6-7—**Topics in Internal Medicine.** Big Sky. Friday-Saturday. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. 406) 657-7083.

March 25-27—**New Developments in Cardiology—Univ. of Wash. Internal Medicine Review Sessions.**

March 25, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 26, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 27, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 22-24—**Congenital Heart Disease in Adults—Univ. of Wash. Internal Medicine Review Sessions.**

April 22, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 23, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

April 24, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 27-29—**Office Endocrinology—Univ. of Wash. Internal Medicine Review Sessions.**

May 27, Wednesday, Great Falls. 5-7:30 p.m. Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

May 29, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 10—**Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

IDAHO

October 20—**Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

October 21—**Inpatient CNS Management—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

October 30-November 1—**Epilepsy (Univ. of Washington).** Contact: U/W CME Division, SC-50, Seattle, WA 98195. (206) 543-1050.

October 30, Thursday, Pocatello. Auditorium, Idaho State University Health Sciences Center.

October 31, Friday, Twin Falls. Magic Valley Memorial Hospital, Conference Rooms A & B.

November 1, Saturday, Boise. St. Alphonsus Hospital, McCleary Auditorium.

November 18—**Pulmonary Disease—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

January 20—**Endocrinology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

February 14-21—**Perinatal Critical Care.** Sun Valley. Saturday-Sunday. Elkhorn Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21-28—**Sports Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 16—**Gyn Oncology—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

March 17—**Infectious Diseases—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 18—**Evaluation and Treatment of Premature Labor—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 19—**Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 9-13—**Twelfth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

MEDICINE

November 13-14—**Symposium on Critical Care Medicine.** Portland, Thursday-Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 23-25—**Northwest Review of Obstetrics & Gynecology.** Portland, Thursday-Saturday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

November 21—**Practical Applications of Ultrasound Scanning to Problems of Clinical Obstetrics.** Portland. Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education. University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OF INTEREST TO ALL PHYSICIANS

October 30-31—**Oregon Medical Association 106th Annual Scientific Assembly.** Hilton Hotel, Portland. Contact: Sondra Gleason, Oregon Medical Association, 5210 SW Corbett Avenue, Portland, OR 97201. (503) 226-1555.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

October 16-17—**Infectious Disease.** Tacoma. Thursday-Friday. Tacoma General Hospital. Contact: CME Pierce County.

October 16-17—**Office Gynecology for Primary Physicians.** Seattle. Thursday-Friday. U/W at Museum of History & Industry. Contact: U/W School of Medicine.

October 18—**Lower Extremity Orthopedics in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Jackie Kersh, Office of Medical Education, Group Health Hospital, 201 16th Avenue East, Seattle, WA 98112, (206) 326-7348.

October 24-25—**Ophthalmology for Nurses and Office Assistants.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

October 27—**Antibiotics and Infectious Disease—U/W Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m. Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

October 30—**Epilepsy.** Pocatello, ID. Thursday. U/W at Idaho State University, Health Sciences Auditorium. Contact: U/W School of Medicine.

October 30-31—**Nosocomial Infections and Their Control.** Seattle. Thursday-Friday. U/W Health Sciences Auditorium. Contact: U/W School of Medicine.

October 31—**Epilepsy.** Twin Falls, ID. Friday. U/W at Magic Valley Memorial Hospital Conference Rooms A & B. Contact: U/W School of Medicine.

November 1—**Epilepsy.** Boise, ID. Saturday. U/W at St. Alphonsus Hospital, McCleary Auditorium. Contact: U/W School of Medicine.

November 6-7—**Current Concepts in Drug Therapy.** Seattle. Thursday-Friday. U/W Health Sciences Auditorium. Contact: U/W School of Medicine.

November 6-9—**United States Section, International College of Surgeons Annual Meeting.** Las Vegas, NV. Thursday-Sunday. Aladdin Hotel. Contact: Franklin R. Smith, MD, 942 Medical & Dental Bldg., Seattle, WA 98101. (206) 682-1944.

November 13-15—**Street Drugs.** Seattle. Thursday-Saturday. Park Hilton Hotel. Contact: Marilyn Carlson, Northwest Hospital Education & Training Dept., 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ex. 686.

November 13-15—**Topics in Emergency Medicine.** Seattle. Thursday-Saturday. Seattle Hyatt House (Sea-Tac). Contact: Joan Palmer, c/o WSHA, 419 Occidental Avenue South, Seattle, WA 98104. (206) 624-7240.

November 13-15—**Alcohol and Other Dangerous Drugs.** Seattle. Thursday-Saturday. Park Hilton Hotel. Contact:

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

Marilyn R. Carlson, Departmental Assistant, Education and Training Department, Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500.

November 14—**Yoeder Lecture—Radiology.** Tacoma. Friday. St. Joseph Hospital. Contact: CME Pierce County.

November 14—**Annual Cancer Conference: Head and Neck Cancer.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

November 17-20—**Immunology-Allergy.** Tacoma. Monday-Thursday. Tacoma General Hospital. Contact: CME Pierce County.

November 18—**Congenital Defects—U/W Pediatrics Sessions** (Spokane). Tuesday. 12:00-1:00 p.m. Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

November 21—**Movement Disorders.** Seattle. Friday. U/W at Museum of History & Industry. Contact: U/W School of Medicine.

November 22-29—**Financial Planning for Physicians.** Maui, Hawaii. Saturday-Saturday. U/W at Maui, Wailea Beach. Contact: U/W School of Medicine.

November 23-30—**New Directions in Psychiatry.** Honolulu, Hawaii. Sunday-Sunday. U/W at The Ilikai, Honolulu. Contact: U/W School of Medicine.

November 24—**Medical Genetics—U/W Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

December 3—**Hyperalimentation.** Seattle. Wednsday. Northwest Hospital Auditorium. Contact: Marilyn R. Carlson, Departmental Assistant, Education and Training Dept., Northwest Hospital, 1511 North 120th, Seattle, WA 98133. (206) 364-0500.

December 4-5—**The Physician, Trustee, and Hospital.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

December 5—**The Cancer Program In Your Community Hospital.** Seattle. Friday. Doubletree Inn. Contact: Donal Sparkman, MD, Washington Division, American Cancer Society, 2120 First Avenue North, Seattle, WA 98109. (206) 283-1152.

December 5—**Specialty Problems in Pediatrics.** Seattle, Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

December 6—**The Nervous System for Attorneys.** Seattle. Saturday. Contact: U/W School of Medicine.

December 9—**Pediatric Endocrinology—U/W Pediatrics Sessions** (Spokane). Tuesday. 12:00-1:00 p.m. Sacred Heart Medical Center: Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

December 11-12—**Aging and Elderly.** Seattle. Thursday-Friday. U/W at Washington Athletic Club, Noble Room. Contact: U/W School of Medicine.

December 16—**Evaluation of Male Fertility—U/W OB-GYN Sessions** (Spokane). Tuesday. 12:00-1:00 p.m. Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, W. 101 8th Avenue, Spokane, WA 99204. (509) 838-8347.

1981

January 16-17—**Beta Blocking Agents/Calcium Antagonists.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

January 23—**The Foot.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

January 23-24—**Developmental Disorders in Children.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

January 24—**New Approaches to Gastrointestinal Bleeding.** Tacoma. Saturday. St. Joseph Hospital. Contact: CME Pierce County.

January 29-30—**Financial Planning for Physicians.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

February 5-6—**Schizophrenia and Depression.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

February 6-7—**Workshops in Fluid and Electrolyte Disorders.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

February 12-14—**National Health Service Corps.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

February 14-21—**Perinatal Critical Care.** Sun Valley, ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Sports Medicine.** Sun Valley, ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Practical Neurology.** Ilikai, Honolulu, Hawaii. Saturday-Saturday. U/W at Ilikai, Honolulu, Hawaii. Contact: U/W School of Medicine.

February 21-28—**Metabolism and Endocrinology.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

February 27—**Diagnosis and Treatment of Common Arthritic Diseases.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 5-6—**Preventing/Surviving Stress as a Physician.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

March 6-7—**Clinical Pharmacology for the Practitioner.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 7—**Handicapped Child.** Seattle. Saturday. Contact: U/W School of Medicine.

March 12-13—**Tacoma Academy of Internal Medicine.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 12-13—**Diabetes in General Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

March 17—**Epilepsy.** Spokane. Tuesday. Contact: U/W School of Medicine.

March 23-27—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

March 26-27—**Sexually Transmitted Diseases.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

March 30-April 10—**Rehabilitation Medicine Review.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

April 3—**Nutrition in the Hospitalized Patient.** Seattle. Friday. Contact: U/W School of Medicine.

April 4—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

April 4-11—**Current Concepts in OB/GYN.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Office Management of Chronic Pain.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Wailea, Maui, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Drug Therapy.** Maui, Hawaii. Saturday-Saturday. U/W at Royal Lahaina, Maui, Hawaii. Contact: U/W School of Medicine.

April 16-18—**Modern Diagnostic Techniques: Use/Abuse.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

April 17-18—**Modern Office Procedures: Minor Surgeries.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

April 18-25—**Emergency Medical Care.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

April 30-May 2—**Trauma.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

May 1—**Management of Acute Medical Problems.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 7-8—**Medical Genetics and Teratology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 15-16—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 15-16—**Medical Alumni.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

May 21-22—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 23-30—**Allergy and Immunology.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

June 4-6—**Radiology Northwest V.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 5-6—**Pacific Northwest Chapter of the American College of Chest Physicians: Cardiopulmonary Symposium.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

June 11-12—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 15-19—**Death Investigation.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

June 18-19—**Respiratory Care.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

July 25-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Saturday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

October 22

SPONSOR: Cottonwood Hospital
TITLE: **Tumor Conference**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

October 24

SPONSOR: Utah Ophthalmological Society
TITLE: **Antivirals and Viral Ocular Disease—Past, Present and Future**
LOCATION: To be announced
FEE: To be announced
CREDIT: 3 hours
CONTACT: A. Thomas Williams, MD (801) 268-6111

October 24

SPONSOR: Hill Air Force Hospital
TITLE: **CT Scan and Ultrasound**
LOCATION: HAFB
FEE: None
CREDIT: 1.5 hours
CONTACT: Harold Jenson, MD (801) 777-3030

November 5

SPONSOR: Cottonwood Hospital
TITLE: **Tumor Conference**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

November 6

SPONSOR: LDS Hospital
TITLE: **Pulmonary Heart Disease Postgraduate Course**
LOCATION: LDSH
FEE: $60.00
CREDIT: 8 hours
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UU: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

November 11
SPONSOR: Cottonwood Hospital
TITLE: **Recent Advances in Hypertension**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

November 19
SPONSOR: Cottonwood Hospital
TITLE: **Tumor Conference**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

November 21
SPONSOR: Cottonwood Hospital
TITLE: **Common Dermatological Problems of Children**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

December 2
SPONSOR: Cottonwood Hospital
TITLE: **Post-Myocardial Infarction Rehabilitation**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

December 10-12
SPONSOR: VeteransAdministration/University of Utah/ American Cancer Society/LDS Hospital
TITLE: **Cancer Update Conference**
LOCATION: Hotel Utah, Salt Lake City
FEE: Non-VA $40.00
CREDIT: 17 hours
CONTACT: Mark W. Wolcott, MD (801) 582-1565

December 12
SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Hypertension**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

1981

January 17-21
SPONSOR: Utah Ophthalmological Society/University of Utah/ Johnson & Johnson
TITLE: **Interocular Lens Course**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 24 hours
CONTACT: A. Thomas Williams, MD (801) 262-6111

January 24-31
SPONSOR: University of Utah
TITLE: **6th Annual Snowbird Radiology Conference**
LOCATION: Snowbird
FEE: To be announced
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8188

January 31-February 7
SPONSOR: University of California, San Francisco, CA
TITLE: **Infectious Diseases in Clinical Practice**
LOCATION: Park City
FEE: $200.00 ($250.00 after October 15, 1980)
CREDIT: 20 hours
CONTACT: Extended Programs in Medical Education
University of California
1308 3rd Avenue
San Francisco, CA 94143
(415) 666-2483 or 666-2894

February 9-12
SPONSOR: University of Utah
TITLE: **10th Annual Family Practice Refresher Course**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 28 hours
CONTACT: David N. Sundwall, MD (801) 581-8633

February 15-20
SPONSOR: University of Utah
TITLE: **Update on Clinical Microbiology and Immunology**
LOCATION: Park City
FEE: To be announced
CREDIT: 24 hours
CONTACT: John M. Matsen, MD (801) 581-5514

February 17-20
SPONSOR: Primary Children's Medical Center
TITLE: **Postgraduate Course in Pediatric Surgery**
LOCATION: Park City
FEE: $250.00
CREDIT: 12 hours
CONTACT: Stan Everett (801) 350-1100

February 20-24
SPONSOR: University of Utah
TITLE: **26th Annual Postgrad Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: 16 hours
CONTACT: Theodore H. Stanley, MD (801) 581-6393

February 21-24
SPONSOR: University of Utah
TITLE: **22nd Annual OB-BYN Course**
LOCATION: Holiday Inn, Park City
FEE: $250.00
CREDIT: 15 hours
CONTACT: David H. Engelberg, MD (801) 581-7647

February 22-27
SPONSOR: Utah Ophthalmological Society
TITLE: **OUS Winter Meeting**
LOCATION: Park City
FEE: To be announced
CREDIT: 12 hours
CONTACT: A. Thomas Williams, MD (801) 268-6111

February 25-27
SPONSOR: University of Utah/Intermountain Pediatric Society/ American Academy of Pediatrics
TITLE: **Common Problems in Pediatrics III**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 16 hours
CONTACT: Bruce Buehler, MD (801) 581-7877

February 25-28
SPONSOR: University of Utah
TITLE: **Gynecologic Oncology Course**
LOCATION: To be announced
FEE: To be announced
CREDIT: 15 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-March 7
SPONSOR: University of Utah
TITLE: **Midwinter Radiology Pacific Cruise Meeting**
LOCATION: Departs from Los Angeles
FEE: $300.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

February 28-March 7
SPONSOR: University of Utah
TITLE: **6th Annual Advances in Internal Medicine**
LOCATION: Snowbird
FEE: $225.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1981—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 22-26, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: 1981—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1981—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1981—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: 1981—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Interim Session: November 14-15, 1980, Kachina Lodge, Taos.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: 1981—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: 1981—date and place to be announced.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Ramada Snow King Inn, Jackson.

February 28-March 7

SPONSOR: University of Utah
TITLE: **Nutrition and Contemporary Medicine**
LOCATION: Park City
FEE: $200.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 7-14

SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 14-21

SPONSOR: University of Utah
TITLE: **3rd Annual Park City Radiology Conference: Neuroradiology**
LOCATION: Park City
FEE: $240.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

April 8-10

SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ University of Arizona Center for Occupational Safety and Health/University of Texas Health Science Center, School of Public Health
TITLE: **3rd Annual Park City Environmental Health Conference: Legal and Ethical Dilemmas in Occupational Health**
LOCATION: Prospector Square Lodge, Park City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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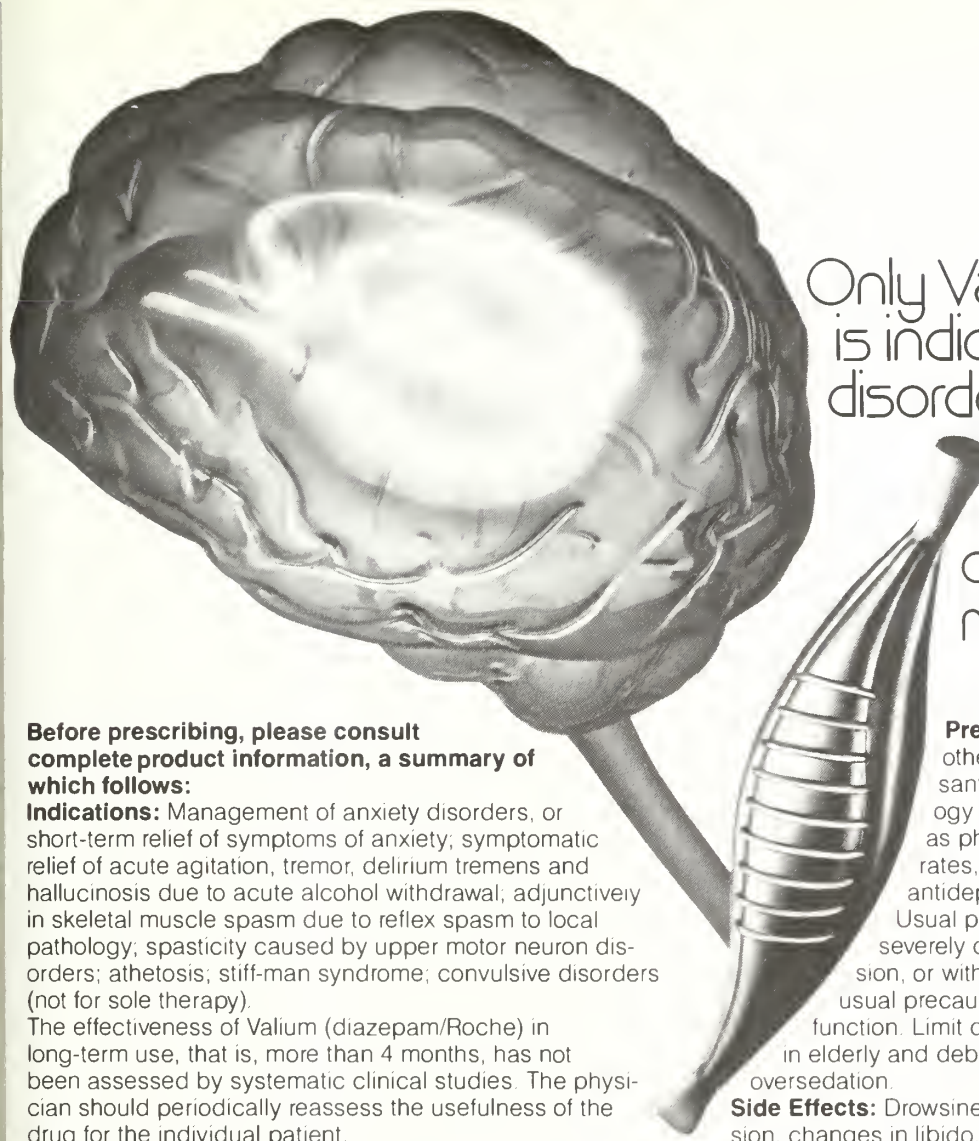

Only Valium® (diazepam/Roche) is indicated in anxiety disorders and as an adjunct in the relief of skeletal muscle spasm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam/Roche) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available in trays of 10.

ROCHE®

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Only Valium® (diazepam/Roche)
has these two distinct effects

mind & muscle

2-mg, 5-mg, 10-mg
• scored tablets

Valium® IV
diazepam/Roche

Indicated in anxiety disorders and as an adjunct in the relief of skeletal muscle spasm.

Please see summary of product information on preceding page.

ROCHE®

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HELVES

THE WESTERN Journal of Medicine

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON
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(See Advertising Page 33)

★★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the Utah State Medical Association and the Washington State Medical Association

The stress-secretion relationship in duodenal ulcer*

The best available evidence suggests that anxiety and emotional tension stimulate acid-pepsin secretion.[1] Also, the development of an ulcer crater in predisposed individuals, or the aggravation of ulcer symptoms, is often typically preceded by a stressful event or situation. *Anxiety* in particular seems to play a determining role in the course and prognosis of the disease, as well as its etiology.

A psychobiologic treatment

To obtain comprehensive relief, many duodenal ulcer patients need more than specific, acid-inhibiting medication—they also need dependable reduction of associated anxiety and emotional tension. With adjunctive Librax you can conveniently give your patient *both* clinical benefits from a single medication.

The pituitary gland plays a key role in the neurohormonal response to emotional stress, leading to an increase in gastric secretion.[2]

1. Isenberg J, Richardson CT, Fordtran Pathogenesis of peptic ulcer, chap. 4 *Gastrointestinal Disease*, ed. 2, edit Sleisenger MH, Fordtran JS. Philad W.B. Saunders Company, 1978, vol. 1 pp. 800, 801.
2. Sun DCH: Etiology and pathology o ulcer, chap. 27, in *Gastroenterology*, edited by Bockus HL, *et al.* Philadel W.B. Saunders Company, 1974, pp. 5

ROCHE

*Librax has been evaluated as possibly effective for this indication.

Please see brief summary of prescribing information on last page of this advertisement.

More than an antisecretory agent... acts on the entire disease entity

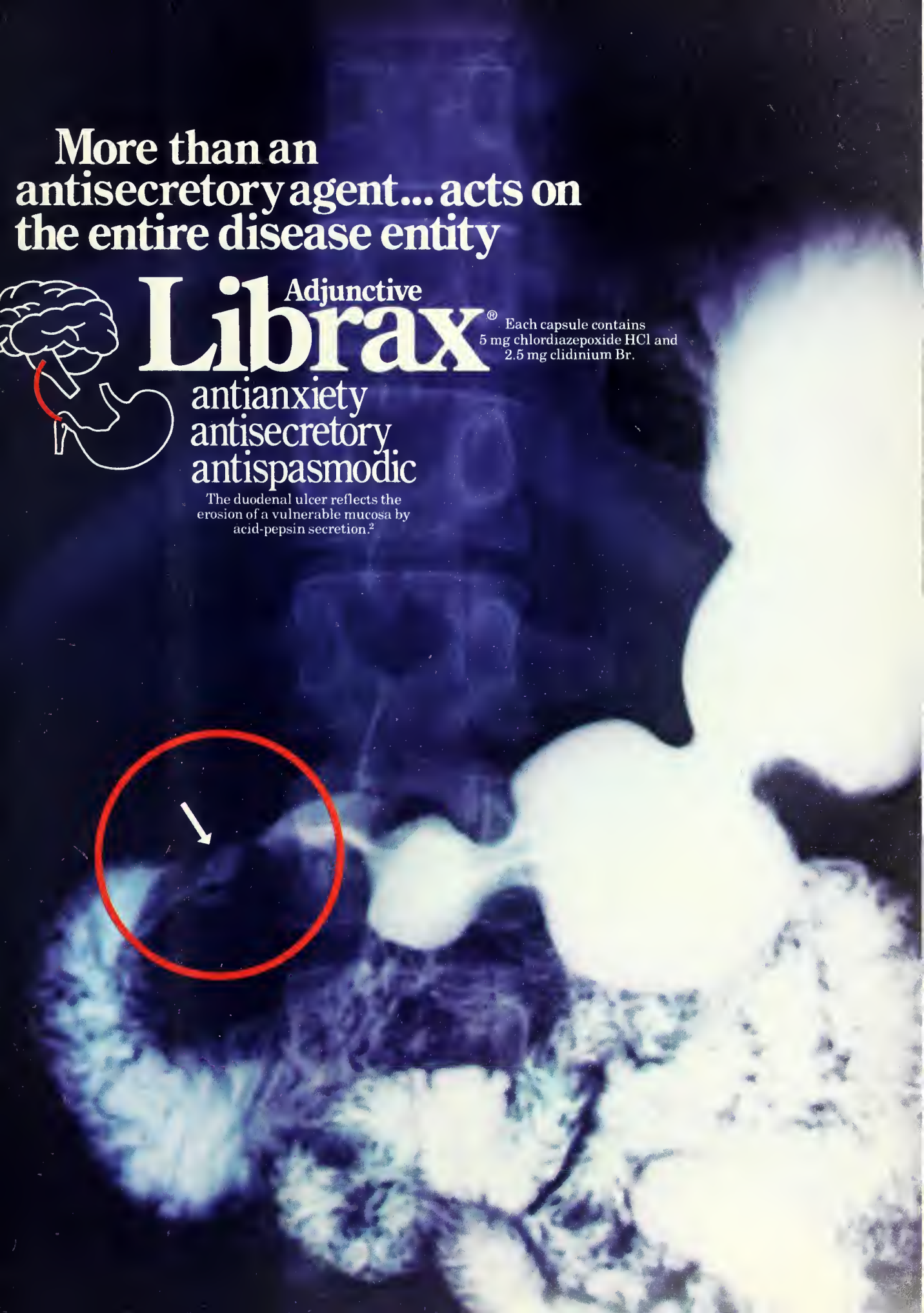
Adjunctive

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

antianxiety
antisecretory
antispasmodic

The duodenal ulcer reflects the erosion of a vulnerable mucosa by acid-pepsin secretion.[2]



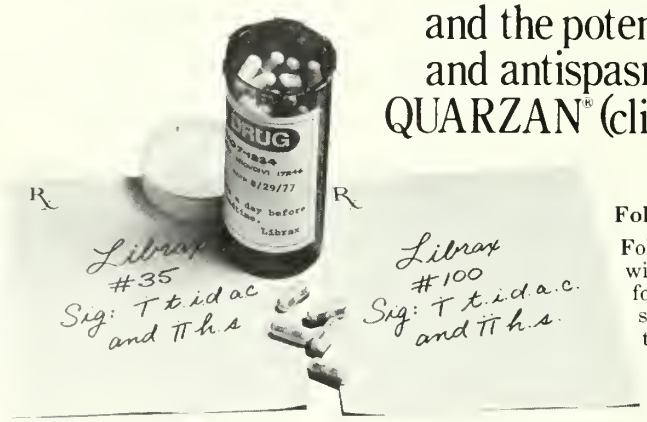
When your duodenal ulcer* patient needs more than an antisecretory agent...

Adjunctive Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

The only duodenal ulcer therapy that provides the specific antianxiety action of LIBRIUM® (chlordiazepoxide HCl/Roche)

and the potent antisecretory and antispasmodic actions of QUARZAN® (clidinium Br/Roche)



Initial Rx

The initial prescription allows evaluation of patient response to therapy.

Follow-up Rx

Follow-up therapy with a prescription for a 2- to 3-week supply of medication usually helps maintain patient gains.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction, hypersensitivity to chlordiazepoxide HCl and/or clidinium Br

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl/Roche) to known addiction-prone individuals or those who might increase dosage, withdrawal symptoms (including convulsions) reported following discontinuation of the drug

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially, increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

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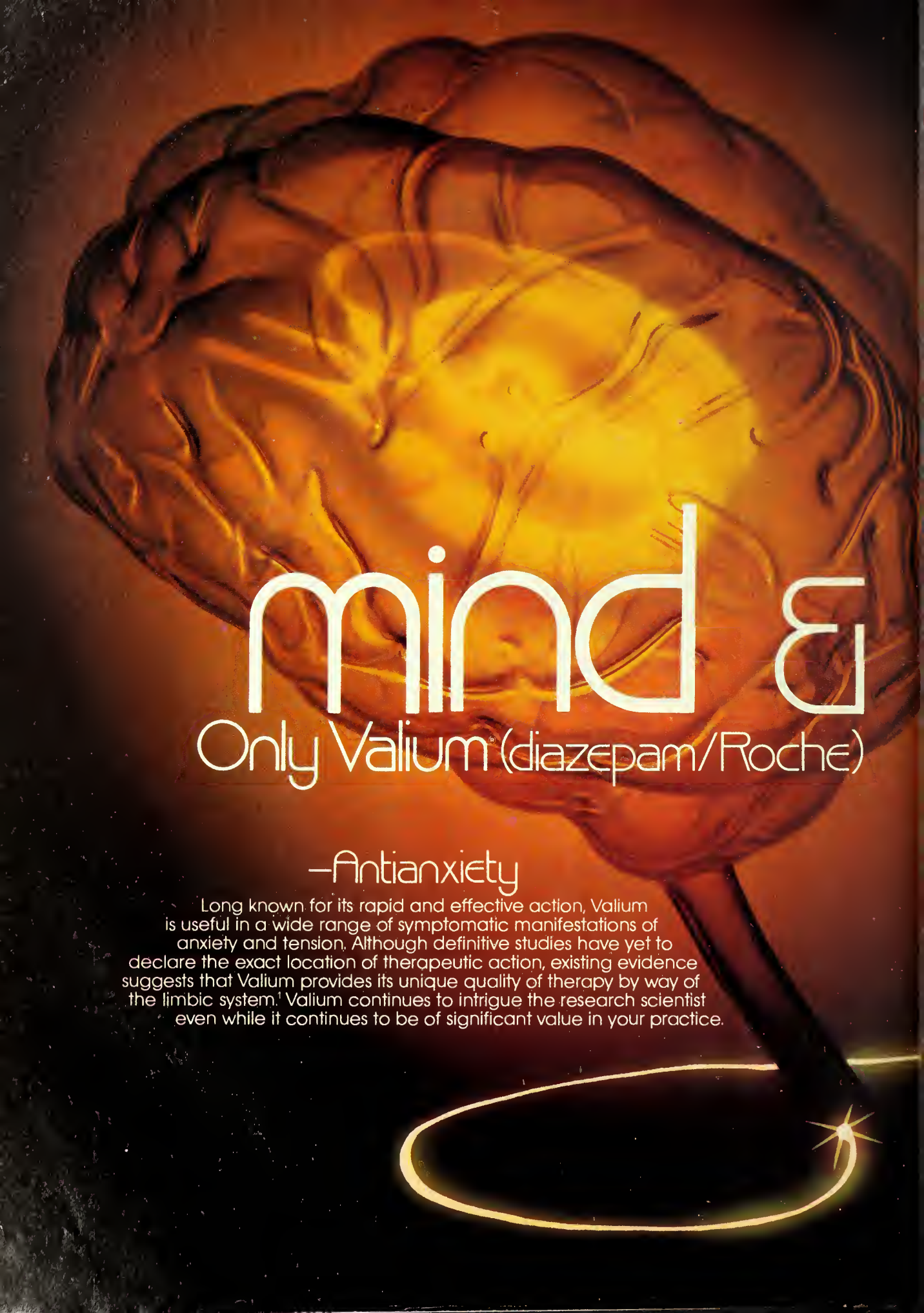
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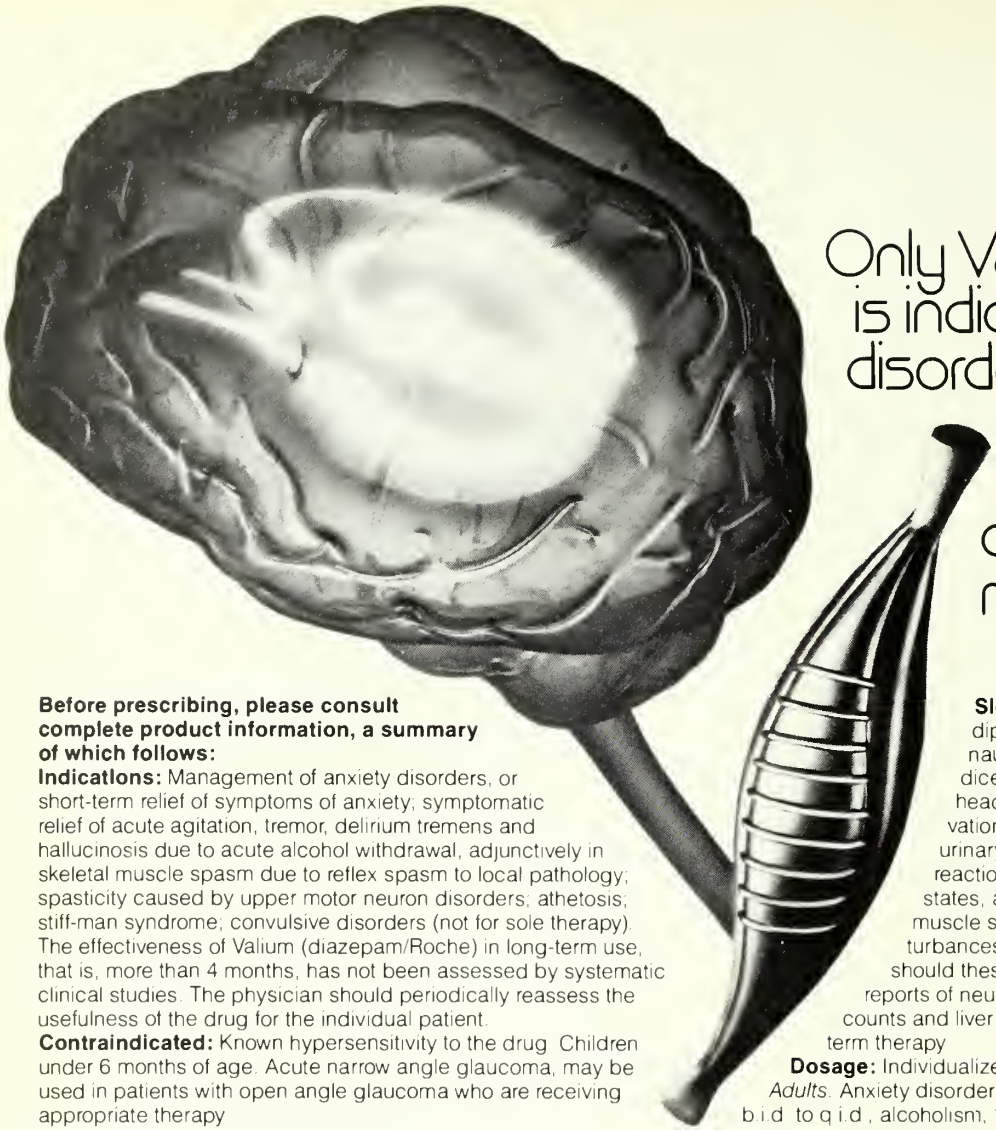

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References:

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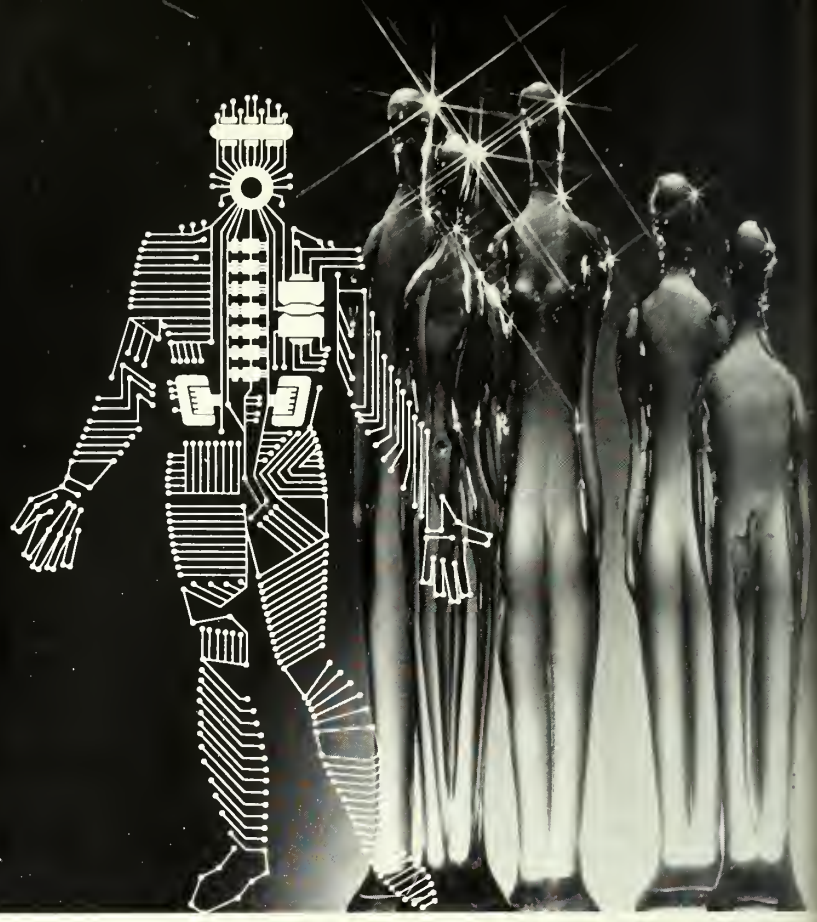

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THE WESTERN
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Refer to: Ganz PA, Vernon SE, Preston D, et al: Lung cancer in younger patients. West J Med 133:373-378, Nov 1980

Lung Cancer in Younger Patients

PATRICIA A. GANZ, MD, *Sepulveda, California;* STEPHEN E. VERNON, MD;
DALE PRESTON, PhD, *and* WALTER F. COULSON, MD, *Los Angeles*

Carcinoma of the lung is rare in younger patients, but occasional reports of this condition have appeared in the literature. This article reviews the clinical and pathological patterns of bronchogenic carcinoma in 96 patients, 40 years old or younger seen at UCLA (University of California, Los Angeles) Hospital between 1956 and 1976. This review confirms the finding in other reports of a higher proportion of women among younger patients with lung cancer as well as a relatively low incidence of squamous cell carcinoma. Using comparative data from the UCLA and California tumor registries, we could find no significant difference in survival of the younger patients when compared with the general population of patients with lung cancer.

CARCINOMA OF THE LUNG occurs most commonly in men in the sixth and seventh decades of life.[1] In our patient population we are also seeing younger patients; many of them are women. Occasional reports of lung cancer in young patients have appeared in the literature.[2-9] Some of these have emphasized the appearance of tumors in the very young,[3] but more often they have dealt with populations younger than 40 or 45 years of age. Several of these reports consider only male patients, and relevant smoking or occupational history has not been included.

The present study was undertaken to review the experience at the UCLA (University of California, Los Angeles) Hospital with bronchogenic carcinoma occurring in male and female patients 40 years of age and younger between 1956 and 1976. We examined clinical presentation, smoking and occupational history, tumor histology and survival in these patients.

Patients and Methods

The UCLA Hospital is a university teaching hospital that was opened in 1956, and serves the greater Los Angeles area as a referral center for difficult diagnostic or therapeutic medical problems. The patient population seen at this hospital has been largely white and middle-class, but medically indigent patients and private patients of local practitioners are also cared for.

The hospital tumor registry routinely reviews and abstracts the records of all patients seen at UCLA with a diagnosis of a malignant tumor. Basic data on each patient (such as age, sex, tumor type) have been stored on computer tape and registry data on specific tumors can be retrieved.

A list of all patients 40 years of age and

From the Division of Hematology/Oncology, Department of Internal Medicine, UCLA School of Medicine, San Fernando Valley Program, Sepulveda (Dr. Ganz); the Department of Pathology (Dr. Vernon), UCLA Cancer Center Base Unit (Dr. Preston) and the Division of Surgical Pathology (Dr. Coulson), UCLA School of Medicine.

Dr. Vernon is a regular Clinical Fellow of the American Cancer Society (CF#4281).

This study was supported in part by a grant from the Brown and Williamson Tobacco Corp.; Phillip Morris Incorporated; R. J. Reynolds Tobacco Co.; the United States Tobacco Company, and the Tobacco Associates, Inc. Computing assistance was obtained from the Health Sciences Computing Facility, UCLA, supported by NIH Special Research Resources Grant RR-3.

Submitted, revised, February 4, 1980

Reprint requests to: Patricia A. Ganz, MD, Division of Hematology/Oncology (111B), Dept. of Medicine, Veterans Administration Medical Center, 16111 Plummer St., Sepulveda, CA 91343.

younger with lung cancer seen at UCLA Hospital between January 1, 1956, and December 31, 1976, was obtained using the Tumor Registry computer file. For the purpose of this report only those cases of bronchogenic carcinoma were included. Nine patients with carcinoid tumors and one with a primary sarcoma were excluded.

Ninety-six patients 40 years of age and younger with bronchogenic carcinoma had been seen during the stated period. Hospital charts, radiotherapy records and tumor registry abstract files were reviewed to obtain the following information: age at diagnosis, sex, race, date of diagnosis, date of death, stage and Karnofsky performance status at diagnosis, smoking and occupational history, and search for another primary source in case of adenocarcinoma.

An attempt was made to review the diagnostic histologic specimen of each patient. Cytologic specimens were not used. Many patients had been referred to UCLA after a diagnostic biopsy was done at their local hospital; some, but not all of these specimens could be obtained for reexamination. We were able to review 61 of the 96 original specimens (64 percent). Autopsy material was reviewed in 23 cases but in 7 of these the original biopsy specimen was not available; therefore, 68 of 96 cases (71 percent) had the pathological diagnosis reviewed.

The specimens were examined by the pathologists without benefit of clinical information. When tissue blocks were available, new sections were cut and appropriate special stains were obtained. A modification of the World Health Organization (WHO) system was used in classifying the lesions. When tissue specimens were not available for reexamination, the pathological diagnosis as initially reviewed by our pathology department was recorded.

Additional comparative data from the entire UCLA Tumor Registry patient population with lung cancer and from the California State Tumor Registry will be used as a basis for comparison.

Clinical and Pathological Findings

Age, Sex and Racial Distribution

In our study group the youngest patient was 25 years old and the oldest was 40 at diagnosis. The median age was 37 years, with the diagnosis made in 40 percent of the patients at age 39 or 40. There was no significant difference in age distribution between the two sexes. In the youngest patient squamous cell carcinoma developed in a previously irradiated field after treatment of Hodgkin disease. The remainder of the patients were between 30 and 40 years old at diagnosis (Table 1). There were 61 men (64 percent) and 35 women (36 percent); the ratio of men to women was 1.74:1. Seven of our patients (7.2 percent) were black; there were no Mexican-Americans.

TABLE 1.—*Age and Sex Distribution of Patients*

Age	*No. of Men*	*Percent*	*No. of Women*	*Percent*	*Total No. of Patients*	*Percent*
25-29 ...	0	0	1	3	1	1
30-34 ...	15	25	7	20	22	24
35-39 ...	34	56	20	57	54	55
40	12	19	7	20	19	20
TOTAL	61		35		96	100

Smoking and Occupational History

Smoking histories were available for 88 of the 96 patients, and 90 percent of these 88 patients either smoked cigarettes or had done so at the time of diagnosis. Nine were nonsmokers and one patient smoked a pipe and cigars. There was essentially no difference in smoking habits between the men and women. Of the 61 men, 52 smoked (85 percent); of the 35 women, 27 smoked (77 percent). About 10 percent of both the men and women stated that they were nonsmokers; no smoking histories were available for the remaining few patients. Of the 78 patients who smoked cigarettes, the quantity of cigarettes smoked each day was available for 75. The median number of cigarettes smoked per day was 26, with a mean of 29. Ninety-five percent smoked 20 or more cigarettes a day and 32 percent smoked 40 or more a day. The length of time patients had smoked was available in 72 cases. The median/mean number of years was 18 (range 5 to 30 years). Only 10 percent had smoked for 12 years or less.

Occupational history was available for 88 patients; 5 of these gave a history of possible carcinogenic exposure. The five patients had the following occupations: silk-screen artist, microwelder, sound technician (with exposure to asbestos), pipe fitter and beryllium miner. Most of the other patients had nonindustrial jobs and were housewives, sales people or office workers.

Symptoms, Weight Loss and Performance Status

Cough, chest pain, hemoptysis and fatigue were the most common presenting symptoms. In 12

TABLE 2.—*Stage at Diagnosis in 94 Patients*

Stage of Disease	*Percent*
Resectable	20
Locally unresectable	40
Metastatic	40

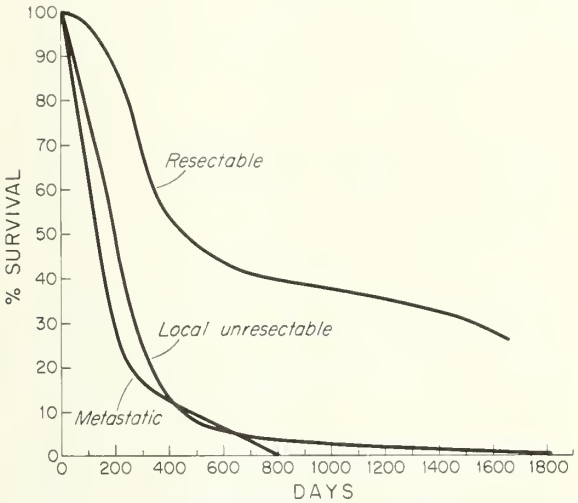

Figure 1.—Actuarial survival curves of patients according to stage of disease at presentation. The curves shown are smooth approximations to the Kaplan-Meier curves.

patients the diagnosis was made because of abnormal findings on an x-ray study of the chest. Information on weight loss was available in 52 cases and the median weight loss was 4.5 kg (10 pounds). The maximum was 33.8 kg (75 pounds) and 17 patients (32 percent) reported no weight loss. Karnofsky performance status could be assessed in only 42 cases. In these patients the median performance status was 78 percent.

Stage at Diagnosis and Treatment

Because this was a retrospective review, exact T,N,M staging (established by the International Union Against Cancer in the UICC *TNM Classification of Malignant Tumours)* could not be used. We have described each patient's stage at diagnosis as being resectable, locally unresectable or metastatic (Table 2). Pleural disease with positive cytologic findings was classified as metastatic, and positive hilar and mediastinal nodes were considered locally unresectable. Some 40 percent of the patients presented with metastasis to distant sites. Thirteen percent of all the patients presented with metastasis to the central nervous system, 5 percent to the liver and 21 percent to the bone.

Twenty percent of patients had operations intended to cure the disease (curative resection). Many others had operations in which only biopsies were done when they were found to have unresectable tumors. Seventy-three percent of the patients received radiotherapy to either the primary tumor or areas of metastatic disease. Chemotherapy was given to 51 percent of the patients.

Pathological Findings

The distribution of the various histological cell types can be seen in Table 3. The relatively low incidence of squamous cell carcinoma is seen in the diagnosis as recorded in the chart, but more strikingly following review. Histological cell types are analyzed according to patients' sex in Tables 4 and 5. Among women there were slightly more cases of adenocarcinoma and fewer of small cell carcinoma. Adenocarcinoma of the lung has been thought to be unrelated to smoking[10]; however, of the 31 patients whose specimens were reviewed and found to have adenocarcinoma, 25 were smokers and 3 were nonsmokers; in 3 no information on smoking was available. Pathological diagnoses in nonsmokers included three cases of adenocarcinoma, one squamous, one undifferentiated and one unclassified.

Survival and Search for Other Primary Sources of Malignancy

The median survival for the entire group of patients was about 27 weeks (190 days). To evaluate any improvements in the diagnosis and treatment of lung cancer which might have occurred during the 21 years of this review, survival was examined before and after January 1, 1966. There were 51 patients seen before January 1, 1966, and 45 patients after that time. For those treated from 1956 to 1965 the median survival was 26 weeks and for those treated from 1966 to 1976 it was 30 weeks ($P=0.55$, chi square $=0.37$ with 1 degree of freedom). When survival was assessed according to stage at presentation, there were 19 patients whose disease was considered resectable; their median survival was 69 weeks. The median length of survival for those with local unresectable disease was 28 weeks, and for those with metastatic disease it was 18 weeks (Figure 1). Survival curves were estimated using the method developed by Kaplan and Meier.[11] Comparisons between survival curves were made with the generalized Wilcoxon statistic developed by Breslow.[12] There was a statistically significant difference in survival for those patients whose disease was resectable compared with those in whom it was not ($P=0.001$, chi square $=17.6$, with 1 degree of freedom). There was no signifi-

cant difference in survival according to sex or pathological type; however, patients 35 years old or younger did better than those 36 to 40 years old (33 weeks survival versus 25 weeks median survival).

There were three long-term survivors (survival greater than five years free of disease) and one patient who died of other causes 14 years after the diagnosis of lung cancer. All four patients had curative resections; one had adjuvant radiation therapy and another required a subsequent resection for localized disease.

Another primary source of malignant disease was sought in 20 cases; this was done primarily in those patients with adenocarcinoma or undifferentiated carcinoma. No other source was found.

Data from the UCLA and California Tumor Registries

Between 1956 and 1976, there were 1,939 patients seen at UCLA with a diagnosis of lung cancer. Since 1968 there has been a steady increase in the number of lung cancer cases seen per year at UCLA, rising from 65 in 1968 to 142 in 1976, and reflecting the increasing incidence of lung cancer in the general population. However, the number of patients 40 years and younger with lung cancer has been relatively stable, ranging from four to six patients each year. Patients in this age range make up 5 percent of the UCLA Tumor Registry population. The median age of patients with lung cancer seen at UCLA was 58 years and the male to female ratio was 2.7:1.

The California Tumor Registry recorded 26,323 new cases of lung cancer between 1956 and 1976. Only 3 percent of the patients were 40 years old or younger. The median age of the population was 62 years and the male to female ratio was 3.0:1.

The median survival for all patients with lung cancer seen at UCLA was six months and in the California Tumor Registry population it was five months. Data from the UCLA and California tumor registries show that younger patients (aged 0 to 40 years) survived slightly longer, with median survival times of 6.3 months and 6 months, respectively.

Discussion

There are many similarities between the findings in our study population and others reported in the literature. In all of the reports that include both men and women there are more women in the younger group than in the general population of patients with lung cancer. The ratio of men to women in these series[4,5,7,8] varies from 3.25:1 to 2:1, in contrast to the general population of patients with lung cancer in which there is a greater proportion of males. Our findings of a male to female ratio of 1.74:1 is consistent with these other reports, while our general tumor registry population of patients with lung cancer had a ratio of 2.7:1. The relative increase in the number of women among the younger patients may reflect the more recent increase in smoking among women (1930 to 1949 versus 1900) and that the population of women at risk for lung cancer is, on the average, younger.[13-15]

Only a few of the series reporting on lung cancer in young patients included data on smoking history.[2,5,6,8] In all of these studies 85 percent or more of the patients were smokers. Kyriakos and Webber[6] reported that in their 27 patients younger than 40 the mean number of cigarettes smoked was 30 (1.5 packs) per day. Similarly, we found that of the 88 patients with available smoking history, 90 percent were cigarette smokers with a mean number of 29 cigarettes smoked per day. Thirty-two percent of those who smoked used 40 or more per day. The number of years our patients smoked (18 years) correlated with their age, as most patients began smoking in their late teen years.

There are some interesting findings regarding the histological type of lung cancer in younger patients. The American medical literature shows a preponderance of adenocarcinoma in these patients,[2,4,6,7,9] with a range in relative incidence of this variety from 30 percent to 46 percent. The British literature[5] suggests an increased incidence of oat cell carcinoma in young patients. This is in contrast to most series of patients of all ages where squamous cell carcinoma is the leading cell type.[16-19] The converse of this observation is that squamous cell carcinoma occurs less frequently in young patients with lung cancer.

The pathological diagnosis recorded in the charts of our 96 patients shows an even distribution among adenocarcinoma, squamous cell carcinoma and undifferentiated carcinoma (Tables 3, 4 and 5). When 68 of the pathological specimens were reviewed using newer classification criteria, the high incidence of adenocarcinoma and paucity of cases of squamous cell carcinoma (irrespective of sex) in these young patients was even more striking. Because specimens were randomly obtained

for review, we feel this is a fair representation of the true histological variation in this group.

Recent reviews of the histology of lung cancer suggest a general trend towards increased occurrence of adenocarcinoma.[20] This increased incidence in younger patients may be a reflection of this more general trend. This is of some importance because the survival of patients with nonsquamous cell carcinoma is shorter in most series.[21,22]

The major issue raised in the literature regarding lung cancer in younger patients is whether or not the disease is biologically more aggressive in this group. Younger patients would seem to have a higher potential for successful resections and cure because they lack serious underlying medical problems that might preclude operation. This same factor, however, may contribute to a delay in seeking medical attention and further delay diagnosis until the disease is more advanced and no longer curable.

TABLE 3.—*Distribution of Histological Cell Types*

Histological Type	*Diagnosis on Chart (96 Patients)*	*Percent*	*Diagnosis at Review (68 Patients)*	*Percent*
Adenocarcinoma	27	28	31	46
Squamous	26	27	6	9
Small cell	6	6	11	16
Undifferentiated	24	25	16	24
Unclassified	10	10	3	4
Unknown	3	3	..	..
Insufficient data for diagnosis	..	..	1	1

TABLE 4.—*Distribution of Histological Cell Types in Male Patients*

Histological Type	*Diagnosis on Chart (61 Patients)*	*Percent*	*Diagnosis at Review (37 Patients)*	*Percent*
Adenocarcinoma	18	30	15	41
Squamous	16	26	2	5
Small cell	4	7	8	22
Undifferentiated	14	23	9	24
Unclassified	6	10	2	5
Unknown	3	4	..	..
Insufficient data for diagnosis	..	..	1	2

TABLE 5.—*Distribution of Histological Cell Types in Female Patients*

Histological Type	*Diagnosis on Chart (35 Patients)*	*Percent*	*Diagnosis at Review (31 Patients)*	*Percent*
Adenocarcinoma	9	26	16	52
Squamous	10	29	4	13
Small cell	2	5	3	10
Undifferentiated	10	29	7	22
Unclassified	4	11	1	3

The rate of curative resections in young patients with lung cancer ranges from 18 percent in Neuman's series[7] to 64 percent in the group of patients discussed by Kyriakos and Webber.[6] The high rate of resection for cure in the latter series can be accounted for by the very aggressive approach taken by the surgeons at Barnes Hospital, St. Louis, as mentioned by the authors. Most series reviewed[2,4,7-9] reported rates of curative resection of between 20 percent and 30 percent. Therefore, the findings of our study, in which 20 percent of the patients had operations with intention to cure, are comparable. The rate of curative resection in younger patients is similar to that in the general population of patients with lung cancer.[23]

Most of the literature on younger patients with lung cancer discusses mean survival times; these range from 4.8 months in Putnam's series[8] to 10.3 months in the series examined by Kyriakos and Webber.[6] These survival rates seemed to be significantly influenced by the number of patients with squamous cell carcinoma in each series (reflecting a more favorable outcome), as well as the percentage of patients who had curative resections. The conclusions regarding survival in each series were directly related to these two factors. The median survival reported in our series was 6.3 months, and this reflects the modest rate of curative resection at our hospital as well as the relatively low incidence of squamous carcinomas in our patient population. After analysis of the survival data from our institution and from the California Tumor Registry, it would appear that the length of survival for younger patients with lung cancer is comparable to that of the general population of patients with lung cancer.

Conclusion

We have reviewed the clinical and pathological findings in 96 cases of bronchogenic cancer in patients 40 years old and younger seen at UCLA Hospital between 1956 and 1976. Our review is in agreement with the literature in finding a higher proportion of women among the younger patients with lung cancer, as well as a relatively low incidence of squamous cell carcinoma in this population. We have confirmed that lung cancer is largely a smoking-related neoplasm among

younger patients. We could find no significant improvement in length of survival among our patients that could be attributed to new therapeutic modalities (chemotherapy and radiotherapy), reflecting the fact that cure of this disease is related to surgical resection. In addition, by using comparative data from the UCLA and California tumor registries, we could find no significant difference in survival of younger patients compared with that of the general population of patients with lung cancer.

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Radiation Therapy for Skin Cancer

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Local control, cosmesis and functional results were evaluated in 315 cases of skin cancer in 247 patients treated with radiation therapy. The initial recurrence rate for basal cell carcinoma was 7.8 percent and for squamous cell carcinoma was 14.9 percent. Ultimate local control was achieved in 98.7 percent of the cases of basal cell carcinoma and in 94.0 percent of the cases of squamous cell carcinoma with use of further irradiation or other therapeutic modalities. Ultimate local control rates were comparable to other therapeutic modalities. Cosmetic and functional results were excellent. Cartilage necrosis was not a significant problem. Radiation therapy may offer advantages in certain clinical situations and should be considered as a mode of therapy in the treatment of skin cancer.

CANCER OF THE SKIN is the most common malignant disease among whites. Its visibility and accessibility usually result in early diagnosis and in a high potential for cure. The characteristics of skin cancer to grow slowly and to metastasize late also enhance therapeutic and cosmetic success.

Theoretically, cancer of the skin can be cured by a wide variety of therapeutic means other than radiation therapy, including surgical excision, electrocoagulation-desiccation, chemotherapy, cryotherapy and chemosurgery.[1-4] In practice, however, this variety raises the possibility of mismanagement, and treatment failures can result in significant morbidity. Neglect or misdiagnosis can result in severe complications and even death.

For optimal results, treatment of carcinoma of the skin should be selected according to the physical characteristics of the lesion and the ability of the physician to carry out the particular therapy.

Radiation therapy of skin cancer has a wide range of indications and great adaptability, but it requires skillful and judicious application. Specifically, there should be adequate quality control of both equipment and calculations of physical factors.

Irradiation of skin cancer should be considered when preservation of normal tissue in certain locations is a concern and other modes of therapy may produce a poor cosmetic result. Radiation therapy offers distinct advantages in selected sites, such as the eyelids, inner and outer canthi, the ears, preauricular and postauricular areas and the nose.

In cases where control can be achieved by several different methods of therapy, that combination providing optimum control and cosmesis should be used.

This report presents 315 cases of cancer of the

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TABLE 1—*Classification of Skin Tumors (Excluding Melanoma)**

T (Primary tumor)
- T_1...Tumor 2 cm or less in largest dimension
- T_2...Tumor 2 to 5 cm
- T_3...Tumor more than 5 cm
- T_4...Tumor with extension to other structures such as cartilage, muscle or bone

N (Regional lymph nodes)
- N_0...No evidence of regional lymph node involvement
- N_1...Evidence of movable homolateral regional lymph nodes
- N_2...Evidence of movable contralateral or bilateral regional lymph nodes
- N_3...Evidence of fixed regional lymph nodes

M (Distant metastasis)
- M_0...No evidence of distant metastasis
- M_1...Evidence of distant metastasis

*Source: Union Internationale Contre le Cancer.[5]

TABLE 2.—*Location of Skin Lesions*

Location	*No. of Lesions*
Face	124
Nose	87
Ear	34
Eyelid	32
Neck	9
Hand	8
Other	21
TOTAL	315

skin in 247 patients treated by radiation therapy at the Radiation Center at the LDS Hospital from 1969 to 1977. An evaluation of local control, cosmesis and functional results is presented.

Patients and Methods

Patient Selection and Evaluation

All patients seen and treated at the Radiation Center for cancer of the skin between 1969 and 1977 were included in the study, and their skin lesions were classified according to the 1978 International Union Against Cancer (UICC) handbook[5] (Table 1).

In all cases requiring subsequent therapy for control of primary lesions radiation therapy was considered to have failed. These cases included both definite infield recurrences or persistence of disease as well as any marginal recurrences. Some marginal recurrences were difficult to evaluate, however, and may have represented separate primary lesions. No patients died during the course of radiation therapy. There were 247 patients with a total of 315 lesions in the study. Of the 315 lesions, 298 were primary lesions and 17 were recurrent lesions. For all patients included in statistical evaluation there was a minimum two-year follow-up period and for most the period of evaluation was longer.

Thirteen patients, with a total of 14 lesions had inadequate follow-up, that is, less than two years' observation following therapy. These patients were not included in statistics defining local control and recurrence rates, although most of these patients had two to three follow-up visits without evidence of recurrence of disease. The remaining 234 patients were evaluated for control of the local lesion, and for cosmetic and functional results. An evaluation was also made for uncontrolled metastasis.

Treatment

Most of the patients were treated with an intended dose of 1,900 ret calculated by the nominal standard dose (NSD) formula according to Ellis,[6] corrected for orthovoltage. Treatment was standard for most patients and consisted of approximately 390 to 400 rad (skin dose) in 10 fractions over 12 to 14 days. This dose was delivered on a 100-kV General Electric Maximar unit with a 1 mm or 3 mm aluminum filter (half-value layer of 1.4 mm aluminum and 2.8 mm aluminum, respectively). Treatment schemes varied somewhat according to extent and location of the lesion. The therapy was modified at the discretion of the radiotherapist and according to the physical characteristics of each particular lesion. Occasionally, the treatment course was prolonged and given with megavoltage equipment. All biopsy specimens were reviewed by pathologists at LDS Hospital and confirmation of the histological diagnosis was obtained before initiation of therapy.

Results

In all, 247 patients with a total of 315 lesions were treated with radiation therapy and evaluated in this study. Of the 315 lesions, 241 were identified as basal cell carcinoma and 71 were diagnosed as squamous cell carcinoma. Of 17 recurrent lesions, 8 were basal cell carcinoma and 9 were squamous cell carcinoma. The remaining three were other histological types consisting of two eccrine tumors and one adenocarcinoma of the skin. The locations of the lesions are presented in Table 2.

Of 231 cases of basal cell carcinoma, 18 failed therapy—a recurrence rate of 7.8 percent; of 67 cases of squamous cell carcinoma, 10 failed

therapy—a recurrence rate of 14.9 percent. This resulted in a total recurrence rate for both types of tumors of 9.3 percent. These results are presented in Table 3. (As mentioned earlier, 13 patients with a total of 14 lesions were not included in these calculations because of inadequate follow-up evaluation.) An analysis of the initial stage of lesions and locations of recurrence in basal cell carcinoma is presented in Table 4. An analysis of similar data for recurrences of squamous cell carcinoma is presented in Table 5.

Of the 18 cases of basal cell carcinoma that failed radiation therapy, two (located on the nose and ear) were recurrent lesions at the time of treatment. The remaining 16 primary lesions were located as follows: nose (6), ear (3), face (4), and lip, eyelid and cheek (1 each). Of ten squamous cell carcinoma treatment failures, five involved recurrent lesions at the initiation of therapy and were located as follows: ear (3) and hand (2). The remaining five primary lesions were located as follows: nose, face, hands, scalp and ear (1 each).

In two patients, recurrences of the primary lesion within the field of treatment were attributed to inadequate radiation therapy. The cause of marginal recurrences was difficult to evaluate and a distinction between persistent disease and a separate primary lesion could not be made with certainty in all patients. In cases in which any doubt was present, therapy was considered to have failed. Both patients with uncontrolled stage T_4 basal cell carcinoma died subsequently as a result of extension of their disease.

Of 14 patients with initial lymph node involvement (stages T_{any} N_1) with squamous cell carcinoma at the time of referral, 4 recurrences were either nodal or metastatic; two patients with uncontrolled carcinomas subsequently died as a result of their disease. Analysis of the 15 cases of stage T_1-T_2 basal cell and squamous cell carcinoma that required further definitive therapy (surgical or radiation) showed that all except one were salvaged by an operation or additional irradiation. The status of this latter patient is unknown. Ultimate local control was achieved in 98.7 percent of cases of basal cell carcinoma and in 94.0 percent of cases of squamous cell carcinoma by additional irradiation or other therapeutic modalities.

Complications of therapy included significant atrophy of the skin, severe induration, contractures of the eyelid, necrosis and a nonfunctioning lacrimal gland (Table 6). Both patients who sustained complications of eyelid contractures after radiation therapy had had previous surgical intervention in that area. Of 121 lesions treated over cartilage, including the nose and the ear, one case of chondronecrosis was observed. Dryness of the eye, resulting from a nonfunctioning lacrimal gland was due to a technical error in treatment.

Comment

Cancer of the skin is an extremely common malignant disease. Early diagnosis enhances the therapeutic and cosmetic success in the treatment

TABLE 3.—*Recurrences After Radiation Therapy**

Type of Carcinoma	*No./Total*	*Percent*
Squamous cell	10/67	14.9
Basal cell	18/231	7.8
Other	0/3	0
TOTAL	28/301	9.3

*Thirteen patients (14 lesions) were not included in calculations because of inadequate follow-up evaluation.

TABLE 4.—*Recurrences of Basal Cell Carcinoma by Stage and Location*

Basal Cell Carcinoma		*Recurrences*			*Salvages**
Stage	*Number*	*Number*	*Infield*	*Marginal*	*Number*
T_1	188	12	7	5	11†
T_2	36	3	2	1	3
T_3	2	..	..	..	..
T_4	5	3	1	2	1

*By further surgical or radiation treatment.
†One patient with status unknown.

TABLE 5.—*Recurrences of Squamous Cell Carcinoma by Stage and Location*

Squamous Cell Carcinoma		*Recurrences*			*Salvages**
Stage	*Number*	*Number*	*Infield*	*Marginal*	*Number*
T_1-T_2	46	4	4	..	4†
T_3-T_4	7	2	2	..	0
T_{any} N_1	14	4‡	..	..	2

*By further surgical or radiation therapy.
†One patient with local control died subsequently of metastatic lesions.
‡Nodal or metastatic.

TABLE 6.—*Complications of Therapy*

Complication	*Number*
Severe atrophy	1
Severe induration	1
Necrosis (ear)	1
Eyelid contracture	2
Nonfunctioning lacrimal gland	1

of these lesions. In theory, this entity can be cured by a variety of therapeutic means, with cure rates often reported of over 90 percent regardless of the mode of therapy. The most common methods of treatment for skin cancer used today include electrodesiccation, surgical excision and radiation therapy. In practice, inadequate or poorly skilled application of any method of therapy can result in therapeutic or cosmetic failures. The most common causes of radiation failure include unskilled or unsupervised treatment, inadequate field size or dose, or both, inappropriate filtration or energy, lack of appreciation of extent or depth of the lesion and lack of proper follow-up. No single mode of therapy is optimal in all clinical situations. The choice of therapeutic mode may depend on location and extension of the lesion and history of previous treatment. When control of the initial lesion can be achieved with equal certainty, the technique which provides better cosmetic effect, ease of application, or both, should be used.

Radiation therapy has a wide range of applications and offers certain advantages in selected sites, especially in extensive lesions. When skillfully applied, this method of treatment can result in the selective destruction of the tumor with preservation of normal structures.

Relative indications for irradiation include primary, previously untreated lesions, especially in sites such as the eyelids, inner and outer canthi, ears, preauricular and postauricular areas and the nose. Radiation therapy is indicated for extensive or diffusely infiltrating lesions in any area; it is also indicated for therapy following excision of any skin tumor where surgical margins are inadequate as well as after excision of any recurrent lesion.[4] Cartilage necrosis is frequently mentioned as a complication of irradiation. In this study and in others,[4,7,8] chondronecrosis was not a significant problem and should not exclude therapy in cartilage-bearing areas.

The purpose of this study was to define local control rates and evaluate cosmetic results of radiation therapy of skin cancer. In 247 patients with 315 skin lesions, control of the local lesion was good and results were comparable to other studies.[1,2,4,7-10] Similar control rates have been achieved with surgical excision, electrodesiccation and chemosurgery.[1-4] Cosmetic results were good to excellent; atrophy, induration and telangiectasia occurred infrequently and were not significant in the vast majority of patients. Ultimate local control was achieved by either surgical excision or further irradiation in most of the patients in whom radiation therapy failed.

When local control rates are similar among a variety of therapeutic modalities, cosmetic and functional results should be important considerations in the choice of treatment to be used.

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Drug Withdrawal Syndromes

A Literature Review

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Drug withdrawal syndromes reportedly have been caused by numerous pharmacological agents, but only a few drugs have been adequately studied in this regard. Criteria for evaluating drug withdrawal syndromes have been proposed. Sedative-hypnotic agents, opiates, corticosteroids, clonidine, tricyclic antidepressant medications and beta-adrenergic blocking agents meet the criteria for such syndromes. Gradual tapering of the dose of these drugs is recommended when therapy must be discontinued. Whether or not other drugs cause rebound reactions is questionable, but caution should be used when discontinuing drugs for which numerous reports of withdrawal syndromes exist.

DRUG WITHDRAWAL SYNDROMES are often mistaken for disease states in clinical practice. This article attempts to clarify the significance of some of these syndromes. The evaluation of drug withdrawal syndromes is difficult. Symptoms resulting from discontinuation of a medication may need to be distinguished from reappearance of disease symptoms or a "catching up" of the basic disease state, which may emerge in the absence of the pharmacological action of the drug. Symptoms not related to the underlying disease, such as those related to continued use of other drugs, may further cloud the issue. The simultaneous discontinuation of multiple drugs, addition of an interacting substance or questionable patient compliance all complicate determining the cause of these apparent drug withdrawal syndromes accurately. Also, psychological dependence may need to be distinguished from physiological withdrawal. For many drugs, only a few cases of withdrawal have been reported. The existence of true drug withdrawal must be shown by (1) a trial of gradual versus abrupt drug termination, (2) the appearance of symptoms more severe than baseline symptoms or (3) the onset of symptoms in newborn infants whose mothers have been taking the drug.

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Alcohol

The alcohol withdrawal syndrome is a manifestation of neuronal excitability. The syndrome is similar to withdrawal from other drugs in that the severity of symptoms depends on the size of the dose taken and the duration of consumption. The abstinence reactions occur in two phases. Minor symptoms such as insomnia, irritability and tremors usually appear within 24 hours of discontinuation, and disappear within 48 hours. A second, more serious phase develops after two to three days in severe cases of withdrawal. It includes hal-

lucinations, convulsions and delirium tremens (DT). Delirium tremens, however, occurs in less than 5 percent of patients in hospital who undergo withdrawal.[1] Rebound thrombocytosis appears during alcohol withdrawal in patients with either normal or depressed platelet counts at admission. Elevated counts begin 5 days after admission, peak between 10 to 15 days, with counts as high as 788,000 per cu mm, and last up to three weeks.[2,3] This was offered as a possible explanation for recurring venous thrombosis and pulmonary embolism in two of five patients.[3] Other causes of thrombocytosis were not evident.

Alcohol withdrawal has been treated with numerous pharmacological agents, primarily phenothiazines, paraldehyde and benzodiazepines. Phenothiazines have a distinct disadvantage in their inability to prevent seizures. Controlled trials and extensive clinical experience have shown the superiority of benzodiazepines over paraldehyde.[4] Thus, the benzodiazepines have emerged as the agents of choice for treating alcohol withdrawal. Among the benzodiazepines, chlordiazepoxide has been heralded as the most effective agent, but no controlled trial is available to support this theory.

Anticoagulant Drugs

As a result of retrospective studies, clinicians believed for many years that abrupt cessation of therapy with anticoagulant drugs caused an increased incidence of sudden deaths, myocardial infarctions and anginal attacks. *Rebound* hypercoagulability with resulting thromboembolism was thought to be the cause.[5] As a result, gradual withdrawal of anticoagulant agents was advocated for approximately 25 years. Recently, however, some practitioners have stopped oral warfarin therapy abruptly without increased prevalence of complications.

In a double-blind, prospective study of 78 patients with anginal symptoms and previous myocardial infarctions (MI's), there were no significant differences in the number of myocardial reinfarctions, thrombotic episodes or sudden deaths between the group of patients in whom phenindione was withdrawn abruptly and the group in whom the drug was withdrawn over six weeks.[6] Abrupt or gradual termination of phenindione therapy after two years carried a greater risk of complications than treatment continued for longer than two years. In two other studies of 134 patients with coronary artery disease, abrupt discontinuation of the drug did not carry a higher risk of thromboembolism than gradual tapering when measured by the prevalence of sudden deaths, deaths after acute MI's or increased symptoms of angina.[5,7] It appears that anticoagulant drugs given orally need not be tapered.

Anticonvulsant Drugs

Except for a few cases of status epilepticus resulting from abrupt withdrawal of phenobarbital, little proof exists of an anticonvulsant withdrawal effect in patients with epilepsy. However, barbiturate withdrawal has precipitated seizures in patients not previously predisposed to epileptic disorders. Documentation of status epilepticus from withdrawal of other anticonvulsant medications, including phenytoin and clonazepam, is lacking.[8] One uncontrolled investigation found that abrupt discontinuation of phenytoin did not precipitate convulsions.[8] Another symptom, acute psychosis, has been reported in two patients in whom anticonvulsant medication was gradually withdrawn.[9] The most conservative management plan suggests a gradual tapering of medication over nine months after four years without seizure activity.[10] Until definitive studies are done, caution should be taken to avoid abrupt discontinuation of anticonvulsant drugs in epileptic patients.

Antipsychotic Drugs

The abrupt cessation of antipsychotic drugs appears likely to induce withdrawal symptoms,[11] usually beginning one to two weeks after withdrawal. These include nausea, vomiting, diarrhea, headaches, perspiration, restlessness, insomnia, rhinorrhea, increased appetite and giddiness.[11-13] The occurrence of symptoms ranged among various clinical studies from 17 percent to 75 percent.[11] Withdrawal from phenothiazine therapy apparently does not induce convulsions.[12] Withdrawal symptoms are not dose or plasma level related.[12]

All antipsychotic medications have central and peripheral antimuscarinic properties. It has been proposed that withdrawal symptoms are due in part to an anticholinergic rebound reaction.[11-13] Agents with the most potent anticholinergic properties, such as chlorpromazine and thioridazine, are associated with the highest rate of withdrawal symptoms.[11,12]

Drug-induced Parkinson disease improves with withdrawal of the drug. However, parkinsonism may develop in a patient in whom an antiparkinson medication and an antipsychotic drug are

abruptly withdrawn simultaneously. The proposed mechanism for this phenomenon is that a temporary exacerbation of Parkinson disease results from an unopposed dopamine-blocking effect of the slowly excreted phenothiazine in the absence of the rapidly excreted antiparkinson drug. Typical symptoms include rigidity, tremors and akinesia. Usually these effects peak in approximately four days but can last for as long as four months.[12]

Withdrawal dyskinesia resembles tardive dyskinesia, but is self-limiting and appears for the first time following discontinuation of antipsychotic drug. Dyskinetic symptoms uniformly appear within a few days of termination of therapy, and may last for 1 to 22 weeks; however, they generally last for 6 to 12 weeks.[12] This condition probably results from a temporary hyperdopaminergic state in the basal ganglia following cessation of antipsychotic dopamine blockade.

Symptoms of anxiety or insomnia resulting from withdrawal of the antipsychotic drug are not easily differentiated from schizophrenic symptoms. Therefore, once the decision is made to withdraw antipsychotic medication, gradual tapering is suggested to reduce the possibility of somatic or extrapyramidal symptoms, as well as a relapse into a psychotic state.[11-13] If treatment with an anticholinergic agent is to be stopped, it should be discontinued several days after antipsychotic drugs are withdrawn. The only trial of abrupt or gradual withdrawal of antiparkinson medication showed that symptoms occurred more often and were more severe following abrupt discontinuation.[14]

Barbiturates

Withdrawal symptoms resulting from discontinued use of barbiturates are well known.[15] The likelihood of these symptoms developing depends on the degree of dependency on the drug before withdrawal, the duration of drug use and the rate at which the drug is metabolized. Patients who are physically dependent on large doses of short- or medium-acting barbiturates are at great risk of suffering major complications upon withdrawal.

Isbell stated that in all subjects who were taking more than 800 mg of pentobarbital or secobarbital daily, minor withdrawal symptoms developed upon discontinuing the drug. These include tremors, weakness, insomnia, sweating and restlessness. In 75 percent of patients taking this dose convulsions developed, and in 60 percent delirium tremens occurred upon withdrawal.[16] Except for rare instances, patients taking 600 mg or less per day of barbiturates exhibit only minor symptoms upon abrupt cessation of their use.

After abrupt withdrawal of the drug, there is a direct relationship between the severity of symptoms and when they begin.[15] Within 24 hours, tremors, weakness, insomnia, diaphoresis, restlessness, headache, malaise, nausea, vomiting, anorexia, dry mouth and deep tendon hyperreflexia may occur. Psychological features that are frequently encountered include apprehension, acute anxiety, irritability and depression.

If a patient has been taking barbiturates in large doses or for a long time, severe neurological symptoms may appear within 24 to 72 hours following their withdrawal. Myoclonic muscular contractions, spasmodic jerking of extremities and grand mal seizures may develop. Hallucinations and delirium may also occur between the third and eighth day. Barbiturate-induced delirium tremens is very similar to alcohol withdrawal DT's. Fever may develop within 36 to 72 hours and progress to severe hyperpyrexia. Normally, fever subsides after three to four days, and usually lasts no longer than a week.[15] These adverse effects may be lethal if treatment is not started within 24 to 72 hours of the last barbiturate dose. These patients may be best treated by persons with experience in handling drug withdrawal.

Phenobarbital is the standard drug for the treatment of barbiturate and sedative-hypnotic withdrawal syndromes.[15,17] Because of its long half-life (approximately four days), phenobarbital provides more constant serum levels than shorter-acting barbiturates. It also appears to cause less euphoria.[18] Once phenobarbital equivalents have been established (Table 1), stabilization on equivalent doses should be maintained for two days, after which a gradual withdrawal at a rate of 30 mg per day may be used.[17] This method is conservative. Other programs have varied the degree of tapering in dosage schedules. For example, rapid detoxification has been suggested, whereby daily decreases of phenobarbital are scheduled to be completed in ten days, regardless of the degree of tolerance.[15] No side effects were reported in 200 patients for whom the latter technique was used.

Benzodiazepine Drugs

The potential for benzodiazepine-induced physical and psychological dependence after continued use of generally prescribed doses (such as

TABLE 1.—*Equivalent Doses of Phenobarbital for Common Sedative-Hypnotic Drugs in Treating Withdrawal Symptoms**

Drug	*Sedative-Hypnotic Dose (mg)*	*Phenobarbital Equivalent Dose (mg)*
Barbiturates		
Amobarbital	100	30
Butabarbital	60	30
Pentobarbital	100	30
Secobarbital	100	30
Other sedative-hypnotic agents		
Chloral hydrate	500	30
Ethchlorvynol (Placidyl)	350	30
Glutethimide (Doriden)	250	30
Meprobamate (Equanil, Miltown)	400-600	30
Methaqualone (Quaalude, Sopor)	250-300	30
Methyprylon (Noludar)	300	30
Benzodiazepines		
Chlordiazepoxide (Librium)	100	30
Chlorazepate (Tranxene)	50	30
Diazepam (Valium)	50	30
Flurazepam (Dalmane)	60	30
Oxazepam (Serax)	100	30

*Table reprinted by permission from Khantzian and McKenna[15] (original data from Smith and Wesson[18]).

20 to 40 mg of diazepam per day) has been recognized.[19] After long-term use of 45 mg of diazepam per day, sudden cessation can produce withdrawal symptoms similar to those associated with long-term use of ethanol or barbiturates, including agitation and confusion.[20] Acute organic brain syndromes, seizures and coma have been reported.[20] Kales stated that rebound insomnia can be induced by the shorter-acting benzodiazepine agents, such as nitrazepam (not on the market in the United States), but not by diazepam or flurazepam.[21] Withdrawal symptoms are minimal for the first five days and peak between the fifth and ninth days. In patients taking large doses (about 300 mg per day) over a long time, the drug should be withdrawn slowly to minimize the likelihood of withdrawal seizures.[19] Gradual withdrawal from large doses should probably begin without interruption of the dosage schedule and continue for ten days.

Psychosis has been associated with sudden withdrawal of benzodiazepine drugs. However, in the cases reported, each patient had a prior history of psychiatric illness.[19,20,22] Generally, the onset of psychosis occurs three to eight days after withdrawal. Doses of less than 45 mg of diazepam per day in patients without histories of psychiatric illness caused minor abstinence syndromes, but no seizures or withdrawal psychoses were noted. Treatment of withdrawal psychosis consists of either readministration of the benzodiazepine agent or instituting pentobarbital as substitute therapy. Pentobarbital is a rapid-acting, sedative-hypnotic drug that produces cross tolerance with the benzodiazepine agent.[19] Reversal of the psychosis usually occurs within 24 to 48 hours as the patient becomes sedated.

Cimetidine

Since its introduction, cimetidine has been widely used in the treatment of gastrointestinal ulcerations and other disease states. In recent case studies abrupt ulcer perforations after cessation of therapy have been reported,[23,24] but rebound hyperacidity has not been shown conclusively. No firm evidence has established that abrupt or gradual withdrawal provokes a rebound effect.[25]

Clonidine

The sudden withdrawal of clonidine (0.2 mg or more per day) may precipitate rebound hypertension in a small percentage of patients. It is postulated that this condition results from excessive catecholamine release and stimulation of central alpha inhibitory receptors.[26] Clinical features include palpitations, headache, irritability and agitation and, occasionally, insomnia, tremors, nausea and severe vomiting. The resulting elevated levels of urinary vanillylmandelic acid and catecholamines as well as the pressor crisis may last as long as 17 days, but usually last for between 24 and 48 hours. Abrupt withdrawal causes blood pressure to increase to baseline, or rebound to pressures as high as 220 to 270 mm of mercury systolic and 140 to 160 mm of mercury diastolic, accompanied by tachycardia.[26,27] This crisis can be managed either by alpha-blocking drugs such as phentolamine or dibenzyline, taken concomitantly with propranolol, or by reinstitution of clonidine. In these circumstances it may be prudent for clinicians unfamiliar with the syndrome to consult with persons having previous experience in handling clonidine withdrawal syndromes. There have been two case reports of rebound hypertension from sudden withdrawal of methyldopa therapy of the same magnitude as occurs with clonidine cessation.[28,29]

Corticosteroids

Suppression of adrenal activity resulting from corticosteroid use is dependent on the dose, duration, frequency, time and route of administration

of the drug. Doses equivalent to 40 mg of prednisone administered for less than five to seven days infrequently result in appreciable pituitary-adrenal suppression.[30] In these instances, corticosteroids can be discontinued without provoking adrenal crisis. Any reduction in dosage, however, may result in exacerbation of the underlying disease.

Intensive, high-dose therapy for 48 hours is often used in the treatment of allergic emergencies, hypoglycemic coma, cerebral edema, vasculitis and other conditions. When the duration of therapy is 48 hours or less, abrupt discontinuation of the drug carries little risk of precipitating an acute adrenal crisis. This may also be true during treatment for up to five days. However, treatment with large doses for five days or more can cause some degree of impairment in the corticotropin stimulation response.[31] In one study, 13 of 14 patients taking 40 to 100 mg per m^2 of prednisone for 5 to 29 days had suppressed adrenal function for 24 hours. In five patients, this effect lasted seven days or more; however, no patient suffered adverse effects. Postmortem examinations have shown a decrease in the weight of adrenal glands in patients who had received corticosteroid therapy for five to ten days.[32] Supraphysiological doses administered for two weeks have disrupted the hypothalamic-pituitary-adrenal feedback mechanism in patients for as long as 12 months.[33] Therefore, it seems prudent to taper the doses of corticosteroids in patients who have received more than 40 mg of prednisone or its equivalent for more than five days. It is less clear whether one should taper these doses in patients who have been given corticosteroids for two to five days.

Prolonged drug therapy is frequently indicated for many diseases such as asthma and ulcerative colitis. Nearly all patients receiving this therapy (more than 15 mg of prednisolone), require gradual withdrawal to prevent acute secondary adrenal insufficiency.[30,33] An inability to respond appropriately to stress may still persist even after gradual reduction in dose. Administration of 15 mg to 120 mg of prednisolone daily for longer than 10 to 14 days may result in prolonged suppression of the hypothalamic-pituitary-adrenal axis.[30,34] However, patients taking less than 20 mg of cortisol or its equivalent (approximately 5 mg of prednisone) generally are able to respond to stress five months after abrupt discontinuation.[33] Alternate day therapy with intermediate-duration corticosteroids does not interfere with stress response. Where the axis has been suppressed the hypothalamic-pituitary complex usually recovers before the adrenal gland's ability to respond.[34] Attempts to hasten recovery with adrenocorticotropic hormone (ACTH) stimulation have been unsuccessful.

Reduction of the daily dose of prednisone by 2.5 to 5.0 mg every three to seven days is a reasonable approach to gradual tapering.[30] This is a cautious approach, which may be preceded by rapid tapering to physiological doses, provided that flares in the disease do not occur. Thereafter, a more gradual approach is required. Rheumatoid arthritis is an exception to this rule, in that exacerbation often occurs secondary to rapid corticosteroid tapering. During periods of minor stress such as a mild infection, an additional 100 mg per day of hydrocortisone or its equivalent (25 mg of prednisone) should be administered. In cases involving major trauma or surgical procedures, the equivalent of 200 to 300 mg per day of hydrocortisone should be given for as long as 6 to 12 months after cessation of long-term corticosteroid therapy.[30]

To ensure that a patient's adrenal status remains intact, one or both of the following tests may be done. After withholding the morning dose, an 8 AM measurement of plasma cortisol is obtained. A level greater than 10 μg per dl implies that the baseline pituitary-adrenal function is adequate. Or, one may administer 250 μg of synthetic ACTH (cosyntropin) after measuring the baseline cortisol level, to determine the rise in plasma cortisol after 30 to 60 minutes. An increase in plasma cortisol levels of greater than 6 μg per dl, resulting in a level higher than 20 μg per dl is considered to be normal. When this response is observed, corticosteroid therapy can be discontinued.[30,34]

Opiates

Opiate withdrawal is rarely life threatening. The severity of withdrawal symptoms depends on the particular opiate used, the dose and duration of use, and the underlying diseases. Although withdrawal symptoms from various opiates are similar, their onset, duration, and severity vary among preparations. Anxiety, yawning, rhinorrhea, lacrimation, diaphoresis, shaking, chills and piloerection (thus "cold turkey"), anorexia, nausea, vomiting and abdominal cramps begin 6 to 12 hours after the abrupt discontinuation of heroin or morphine.[35] Then after 48 to 72 hours, central nervous system excitation, restlessness,

insomnia, muscle spasms, and low back pain occur. Elevated blood pressure, tachycardia, dehydration, ketosis and leukocytosis are common. Symptoms usually subside in five to ten days.

The meperidine withdrawal syndrome begins within 3 hours, peaks in 8 to 12 hours, and lasts three to five days. Apparently, in meperidine withdrawal there are fewer gastrointestinal symptoms; but more severe symptoms of restlessness and muscular twitching than from other opiate abstinence syndromes.[36] The longer-acting methadone produces symptoms beginning 36 to 72 hours, peaking in intensity in 6 days, and subsiding 10 to 14 days after drug discontinuation. The withdrawal syndrome has also occurred in patients who have abstained from high-dose pentazocine,[37,38] or propoxyphene use.[39,40]

In deciding on specific interventions to treat opiate withdrawal, methadone is the drug of choice because of its ability to block the symptoms without producing euphoric effects.[17] Others have used diazepam, chlorpromazine and LAAM (l-α-acetylmethadol) to manage opiate withdrawal symptoms.[41]

To stabilize the condition of a patient who is suffering from withdrawal symptoms, 10 to 20 mg of methadone should be given orally every two to six hours as symptoms persist. It is not unusual to find that 80 to 180 mg per day are needed as an initial stabilization dose. This initial dose should be maintained for two to three days. Also, 1 mg of methadone can be substituted for 4 mg of morphine, 2 mg of heroin or 20 mg of meperidine.[42]

The length of time provided for a gradual tapering of methadone varies among health centers. Prolonged withdrawal has been accomplished by reducing the methadone stabilizing dose by 20 percent each day.[17] Patients taking smaller doses (40 mg per day) can proceed with daily reductions of 5 to 10 mg increments without complications.[15] Complete, gradual withdrawal in patients who have been receiving more than 100 mg per day may take as long as a month. Most health centers use the gradual withdrawal method in one form or another.

Methadone should be withdrawn gradually because its use produces physical dependence. The symptoms induced by methadone withdrawal are similar to those of the other opiates and begin 36 to 72 hours after discontinuance. Methadone withdrawal differs from withdrawal from other opiates in that the former does not produce muscle aches, cramps, signs of autonomic dysfunction, nausea or vomiting. Reports conflict concerning the difference in severity of withdrawal symptoms between methadone and other opiates—some claim that methadone has more gradual and less severe symptoms than other opiates,[17] while others state that methadone produces excruciating withdrawal symptoms greater than other opiates.[43] Recent literature has suggested that the withdrawal symptoms from methadone are more severe than those from heroin, especially in newborn infants.[44]

Circumstances such as arrest or admittance to hospital have led to abrupt cessation of methadone maintenance therapy. In some patients, no symptoms occur after such sudden termination,[45] while in others generalized pain and insomnia have been reported. Almost no symptoms are present two weeks after withdrawal.

The most serious opiate withdrawal symptoms occur in newborn infants of addicted mothers. The onset of withdrawal is determined by the following factors: (1) the time of drug administration before delivery, (2) the amount of the drug consumed, (3) the presence of other drugs in the mother's serum and (4) the metabolism and excretion of the opiate by the infant. Not all infants will suffer withdrawal symptoms. The prevalence of this phenomenon has been estimated to be between 50 percent and 91 percent.[46,47] Symptoms of heroin withdrawal usually begin in the first 24 to 48 hours, while signs of methadone withdrawal can begin during the first four days of life. Careful monitoring of newborn infants is necessary because symptoms may be mild during the first few days, and progress in severity between the 7th and 14th days.

Heroin and methadone cause similar withdrawal symptoms in newborn infants. They can include abrasions, clonus, pronounced tremors, convulsions, decreased sleep time, vomiting, high-pitched cry, respiratory distress and fever. Severe symptoms can lead to profuse vomiting, dehydration with acidosis, and death. Infants of mothers addicted to methadone usually suffer more severe and prolonged symptoms compared with infants of mothers addicted to heroin.[44,46,47] The prevalence of seizures seems to be greater for infants withdrawing from methadone. Among 384 infants of heroin-addicted mothers, only 8 were observed to have seizures, while in 46 infants of methadone-addicted mothers, 5 had seizures.[47] Mortality has ranged between 34 percent and 93 percent.[44] The latter figure represents untreated

infants. Signs of pentazocine withdrawal occur 10 to 20 hours after birth,[38] approximately the same onset as propoxyphene-induced complications. Several treatment protocols have been established involving a variety of drugs, including paregoric, chlorpromazine, diazepam and phenobarbital. The discussion of each treatment modality is beyond the scope of this paper; however, these regimens have been fully described elsewhere.[44,46,47]

Propranolol

The existence of a rebound phenomenon associated with the abrupt cessation of propranolol in patients with coronary artery disease has been supported and denied.[48-50] Abrupt withdrawal in patients taking 80 to 320 mg per day was reported to cause an increased prevalence of chest pains, arrhythmias, acute myocardial infarctions and sudden death.[49] In one double-blind study involving 20 patients with stable angina pectoris, abrupt withdrawal resulted in one fatal myocardial infarction, one episode of ventricular tachycardia and four cases of increased anginal symptoms. The withdrawal phenomenon was more prominent in patients who had gained the most antianginal benefit from the drug and who exhibited the most severe initial symptoms. Abrupt withdrawal of a placebo resulted in anginal symptoms in 4 of 14 patients.

One retrospective study involved 102 patients who had taken at least 80 mg per day for three months or more and who had had catheterization.[48] The results failed to show any significant difference in the prevalence of death or MI's, or significant change in chest pain between a group withdrawing from propranolol use and a control group in whom propranolol therapy was continued. It appears that the actual prevalence of a rebound phenomenon is unknown. A possible rebound reaction may be clouded by intensified symptoms induced by changes in physical exertion.[49]

Shenkman and co-workers reported three cases of hyperthyroidism developing in a group of patients with no prior history of thyroid disease 1 to 12 weeks after discontinuation or reduction in dosage of propranolol.[51] Withdrawal tachycardia, sweating or tremors correlated with increases in serum triiodothyronine (T_3) in another study.[52]

The mechanism of a rebound reaction has not been fully elucidated. Several possible explanations include (1) stimulation of hypersensitive beta-adrenergic receptors,[53,54] (2) a shift of oxyhemoglobin dissociation (favorable rightward displacement occurs with propranolol), (3) reactivation of the renin-angiotensin-aldosterone mechanism, (4) increased platelet aggregation[48] or (5) an increased sympathetic tone unmasked on cessation of beta blockade. Nattel and co-workers observed that in some patients a hypersensitivity to the chronotropic effects of isoproterenol beginning four days after propranolol treatment was precipitously discontinued, and lasting six days (mean values).[54] This hypersensitive response may be due to increased numbers of adrenergic receptors acquired during propranolol therapy, to increased responsiveness of receptors or to elevated plasma catecholamine concentrations. This hypersensitivity appears to be the most plausible mechanism for the propranolol rebound reaction at this time, although each explanation may play a role in the development of the syndrome. Other mechanisms have not been explored as extensively as the hypersensitivity phenomenon.

Generally, propranolol is discontinued abruptly 12 to 48 hours before surgical procedures to avoid additive myocardial depressant effects with anesthetic medication. Few adverse effects resulting from this practice have been reported.[55] In patients with severe coronary artery disease who require cardiac procedures, however, tapering the dose of propranolol over a few days seems reasonable. Other beta-blocking agents have also been reported to cause the rebound phenomenon.

Stimulants

The abstinence syndrome associated with amphetamines, methylphenidate and fenfluramine is marked by lethargy, sleep disturbances and prolonged depression.[15,56,57] Depression is perhaps the most significant symptom; admittance to hospital and therapy with tricyclic compounds generally have been advocated. Use of tricyclic antidepressant drugs in treating patients who are not in hospital and who are known to be drug abusers may be hazardous, however. No controlled study has definitely shown that the tapering of stimulants reduces the severity or duration of withdrawal symptoms.

Tricyclic Antidepressant Medication

Abstinence symptoms due to tricyclic compounds have been reported most often after the abrupt withdrawal of imipramine.[58-61] Only a few case reports have described withdrawal from

desipramine[59] and amitriptyline.[62] Administration of 75 to 375 mg per day of imipramine and 30 to 50 mg per day of amitriptyline for at least two weeks provoked symptoms when abruptly terminated. Symptoms invariably occurred within 24 to 48 hours. The occurrence of withdrawal symptoms in 45 patients was as follows: nausea with or without vomiting in 16, headache in 10, giddiness in 10, chills in 6, weakness and fatigue in 5 and musculoskeletal pain in 4.[61] Of 26 patients treated with imipramine for longer than two months, 22 reported symptoms after discontinuation, while only 3 of 19 patients treated with the same dosage range for less than two months reported similar symptoms on discontinuation of treatment. In one group of 13 patients in whom imipramine therapy had been tapered in less than two weeks, 8 had pronounced and 5 had minimal symptoms. In another group of 13 patients drug doses were tapered for longer than two weeks. In two patients pronounced withdrawal symptoms developed; none complained of mild symptoms. It appears, then, that tricyclic compounds should be tapered over no less than two weeks.

An akathisia-like syndrome has been reported with discontinuation of imipramine use in several patients.[60] This consisted of anxiety, motor restlessness and inability to sit still, which was indistinguishable from akathisia induced by antipsychotic agents. This syndrome appeared when imipramine therapy was abruptly stopped, and disappeared when therapy was reinstituted.

Withdrawal symptoms have appeared in newborn infants of mothers taking tricyclic drugs. Symptoms include breathlessness, cyanosis, tachypnea, tachycardia, wakefulness, irritability and profuse sweating, and develop one to five days after birth. The mothers reported taking 50 to 150 mg of tricyclic drugs per day throughout their pregnancies.[58]

Other Drugs

Other drugs have been reported to cause withdrawal symptoms, but do not meet the criteria listed above. These include azathioprine,[63,64] baclofen,[65,66] cromolyn,[67,68] nitroprusside,[69] antithyroid drugs,[70,71] aminocaproic acid,[72,73] methaqualone,[74] lithium[75,76] and phenelzine.[77]

Conclusion

Although many drugs are considered to cause withdrawal syndromes, few have been adequately studied in this context. The sedative-hypnotic agents, corticosteroids, stimulants, clonidine and tricyclic antidepressant drugs have met one of the criteria for drug withdrawal syndromes as listed above. Other compounds have been reported to cause rebound symptoms in limited numbers of cases. Until further experience bears out that abstinence syndromes result from these agents, no definite recommendations for drug discontinuation (such as before operations or drug holidays) can be made. Nonetheless, precaution should be taken when terminating therapy with drugs for which numerous reports of rebound phenomena exist.

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Macroamylasemia and Other Immunoglobulin-Complexed Enzyme Disorders

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Macroamylase is a circulating complex of immunoglobulin linked to normal amylase in most cases. Its physical properties are heterogeneous, but its large size impairs renal filtration. Macroamylasemia usually causes hyperamylasemia and an amylase clearance:creatinine clearance (C_{AM}:C_{CR}) ratio of less than 1 percent. Macroamylasemia occurs in 2.5 percent of hyperamylasemic patients, and 1 percent of apparently healthy subjects with normal amylase levels. It often accompanies diseases of aberrant immunity or conditions in which pancreatitis must be ruled out. This disorder should be considered in a patient with asymptomatic hyperamylasemia because its detection can obviate a prolonged diagnostic workup. The condition requires no treatment and may be transient. Macroamylasemia is one of several immunoglobulin-complexed enzyme (ICE) disorders. MacroLDemia, an ICE disorder of lactate dehydrogenase (LD), shares features with macroamylasemia. These and other ICE disorders appear to represent nonspecific dysproteinemic responses to disease.

A PATIENT WITH unexplained hyperamylasemia is often subjected to numerous and expensive blood tests, procedures or even laparotomy. A frequently overlooked cause of hyperamylasemia is macroamylasemia, although macroamylase can be assayed in ten minutes.[1] Macroamylase, a macromolecular complex with amylase activity, whose size prevents renal filtration and clearance, occurs in 2.5 percent of patients with hyperamylasemia and 1 percent of the general population. Its presence was first discovered by Wilding and coworkers[2] in 1964 and designated "macroamylasemia" by Berk and colleagues[3] in 1967.

Macroamylasemia involves an immunoglobulin-amylase complex in most cases and possibly a polysaccharide-amylase complex in a few others. It can occur transiently during acute illness or chronically during prolonged illness, and may be present even when serum amylase activity is within normal limits. Macroamylasemia may reflect disease-induced dysproteinemia or may represent an early marker of systemic disease in some patients. The discovery of this disorder has

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ABBREVIATIONS USED IN TEXT

C_{AM}:C_{CR} = amylase clearance:creatinine clearance (ratio)
CK = creatine kinase
EDTA = ethylenediaminetetraäcetate
HES = hydroxyethyl starch
ICE = immunoglobulin-complexed enzyme (disorder)
LD = lactate dehydrogenase
MacroLD = macromolecular lactate dehydrogenase
MW = molecular weight

generated new questions about the human immune system and the body's response to disease Because of recent advances in the understandi g of macroamylasemia and other less frequent immunoglobulin-complexed enzyme disorders, these conditions are reviewed below.

Macroamylasemia

Physical Properties of the Macroamylase Complex

Macroamylase is heterogeneous in its physical properties. It can be clearly distinguished from normal amylase by chromatography, ultracentrifugation and electrophoresis. Normal serum amylase can be dissociated from the macroamylase complex in some cases through acidification.

Chromatography

Normal serum amylase has a molecular weight (MW) of 45,000[4,5] and elutes from a Sephadex G-200 gel column with cytochrome C, whose MW is 13,000. The sedimentation coefficient (which is roughly proportional to MW)[6] of cytochrome C is 4.5 Svedberg units (S).[1] Macroamylase complexes have been recovered from Sephadex G-200 at all positions from 7S to 19S.[1,3,7-31] With Sephadex G-100, macroamylases generally emerge at or near the void volume.[1,2,21,32-37] Dextran gels are inadequate to estimate the MW of a macroamylase complex because macroamylase interacts with the gel, partially dissociating into smaller complexes, plus free amylase.[1,13,15,16,20,21,38] Gel permeation chromatography of free amylase at 4°C on dextran appeared to lead to formation of macroamylase in one study[13] but not in another.[16] Polyacrylamide gel has been used for chromatography,[11,13,15,38-44] but may be more difficult to use than dextran.[15] Agarose gel has also been used successfully.[20] Gel filtration in a reducing solvent has been employed to estimate molecular weights of protein better by eliminating molecular interactions.[45] This procedure, however, partially[29] or completely[20] eliminates the amylase activity of macroamylase, which complicates subsequent assays.

Ultracentrifugation

Ultracentrifugation of human serum can purify macroamylase complexes.* Normal serum amylase has a sedimentation coefficient of 4.5S, and macroamylase complexes have been identified at all positions from 7S to 19S by this method, with most of them at 7S or 11S. In one series,[16] 4 of 22 patients had macroamylase complexes with sedimentation patterns too broad to be assigned a specific S value. In each patient's serum, there may have been a family of macroamylases, each with its own S value.

Electrophoresis

Macroamylase can be distinguished from normal serum amylase using electrophoresis,† but it lacks a specific migration pattern. Normal serum amylase can be fractionated electrophoretically into a slowly migrating and a quickly migrating component[27,48,51]; the former corresponds in position to the amylase in pancreatic extracts, while the latter coincides in position with parotid gland amylase. Macroamylase migrates differently from both of these isoenzymes when using an appropriate matrix such as cellulose acetate,[33,36,39,49,50] polyacrylamide,[3,29,48] or agar,[27,28,33] but not paper (32 of 33 macroamylasemic sera tested).[2,3,10,52] Macroamylase has been observed to migrate both slower[2,3,27-29,33,36,41,48] and faster[27,39,49,50] than pancreatic amylase. At least seven salivary and three pancreatic isoamylases have been distinguished electrophoretically.[53] Additional amylases can arise during diseases that affect the liver, lungs and genital tract,[54] although it is not clear whether these represent posttranslational modifications of the two basic gene products or additional genes.[54-56] Thus, the presence of an "abnormal" electrophoretic band with amylase activity cannot necessarily be assumed to represent macroamylase, especially when the electrophoretic behavior of amylase is so variable.

Dissociation

Specific antigen-antibody reactions may dissociate in acid.[57] Macroamylase complexes have been

*References 7, 10, 13, 15, 16, 20, 22, 46, 47.
†References 2, 3, 27-29, 33, 36, 39, 41, 48-50.

dissociated by acid into amylase monomers with normal properties in most,* but not all[13,15,29,38,60] cases tested. The kinetics of dissociated amylase are indistinguishable from normal amylase.[7,11] Susceptibility to acid dissociation may be inversely proportional to complex size.[15] Dissociation varies in alkali[50,61] and is complete in urea.[11] In 30 percent ammonium sulfate [$(NH_4)_2SO_4$] macroamylase and gamma globulins are insoluble, whereas normal amylase is soluble.[20] *Bacillus subtilis* contains a macroamylase, consisting of divalent ion-linked amylase monomers, that is reduced to monomers by the chelating agent ethylenediaminetetraäcetate (EDTA)[62]; human macroamylase is not dissociated by EDTA,[7,8,10,11] and no experiment has shown polymerization of human amylase.

Nonspecific covalent disulfide bonds can form between globulins and circulating proteins in patients with paraproteinemias.[63] Mercaptoethanol dissociates covalent bonds and can dissociate 11S polymeric immunoglobulins to 7S monomers.[64] The 11S macroamylase in one patient was converted completely to a 7S macroamylase by mercaptoethanol.[7] Other experiments with this reducing agent have been inconclusive.[11] There is no evidence for covalent binding of amylase to other proteins.

Composition of Macroamylase

Most macroamylase complexes contain immunoglobulin complexed with normal amylase. IgA and IgG macroamylases have been observed. The composition of macroamylase is heterogeneous, and there is also evidence that polysaccharides and other proteins can be linked to amylase in some patients.

Immunoglobulin-Complexed Amylase

When macroamylasemic serum, or the amylase-free protein fractions from dissociated macroamylase, are mixed with normal serum amylase, a macroamylase complex is formed in most,† but not all[3,7,11,24] cases tested. The binding substance itself was first shown to be an immunoglobulin in 1968 when Levitt and Cooperband[7] reported a patient with an 11S macroamylase that was precipitated with anti-IgA antiserum. Since then, using immunoprecipitation and immunoelectrophoresis, 23 patients with IgA‡ and 12 patients with IgG[20,27,33,50,54,61] macroamylase have been reported. Two other macroamylases have been found to contain both IgA and IgG.[30,61] No IgM, IgE or IgD macroamylases have been found.

Immunoprecipitation studies of papain-digested macroamylase place the binding site for amylase in the Fab portion of the immunoglobulin and not the Fc portion.[19,50] Of 19 patients in whom the light chain has been identified, the light chain was exclusively kappa in nine and exclusively lambda in ten.[50,61] Immunoprecipitation may not detect globulins bound to amylase if they are cross-linked by disulfide bonds.[50]

Macroamylase immunoglobulins have variable affinities for the amylase of different species as well as for human pancreatic and parotid isoamylases. Levitt and co-workers[38] showed variable binding of four macroamylasemic sera to amylase from baboon and hog, but none to *Aspergillus* amylase. One patient who had been receiving hog pancreatic supplements had a higher molar affinity for hog amylase than human amylase, suggesting the possibility that he had become sensitized to the hog antigen and was producing IgA in the intestinal tract that cross-reacted with his own circulating amylase. Normal serum amylase is 44 percent to 73 percent S-type (salivary), and the remainder is P-type (pancreatic).[60] In a series of 30 macroamylasemic patients, the median percentage of S-type isoamylase in released amylase was 84 percent, with a range of 11 percent to 100 percent.[59] The binding substance in 26 of these cases had a higher affinity for S-type than P-type isoamylase. Kanno and Sudo[50] similarly studied five patients with macroamylasemia and reported higher S-type affinity in one and did not specify relative affinities in the others. Whether immunoglobulin binds at or away from the active site of amylase is not yet known.

Polysaccharide-Complexed Amylase

A synthetic macroamylase can be generated by mixing glycogen with human[12,13] or hog[68] amylase. Concanavalin A (Con-A) precipitates branched polysaccharides and has been shown to dissociate both uncharacterized macroamylase complexes[12,13] and documented immunoglobulin-amylase complexes.[50] It has precipitated one macroamylase complex[29] and not affected another.[13] In three patients soluble starch produced temporary dissolu-

*References 7, 10, 11, 13, 15-18, 20, 22, 26, 27, 38, 40, 50, 58-60.
†References 3, 8, 13, 16, 18, 20, 22, 27, 29, 38, 50, 60, 65, 66.
‡References 7, 18, 26-28, 31, 41, 46, 50, 54, 61, 67.

tion of macroamylase that was reversed after the starch was hydrolyzed.[29] Macroamylase was unaffected by other substances, including heparin,[12] dextran,[12,29] gelatin[29] and sucrose.[29] Thus, there are data suggesting that in some cases of macroamylasemia, amylase is bound at the active site by a polysaccharide or glycoprotein.

Additional evidence of macroamylase heterogeneity, not necessarily suggestive of polysaccharide binding, includes the failure to detect immunoglobulin linkage in 15 cases,[10,22,24,29,33,38,46,61] dissociation at neutral pH in two assays,[21,29] which is not characteristic of an antigen-antibody complex,[57] and incomplete or absent dissociation at acid pH.[13,15,29,38,60] A case of amylase complexed with α_1-antitrypsin has been reported,[33] but the physical properties of this macroamylase were not described.

Methods for Detecting Macroamylase

The definitive demonstration of an amylase complex with an abnormally large molecular weight requires fractionation of serum proteins by size and an assay of each fraction for amylase activity. Direct identification of macroamylase requires chromatography or ultracentrifugation. Gel chromatography can be adapted to a microcolumn or thin-layer filtration assay for rapid screening of sera. Indirect macroamylase assays such as the temperature-sensitive amylase activity assay, electrophoresis and isoelectric focusing, may be useful for mass screenings but may also be inaccurate in an individual patient. The pancreatic scan should not be used in macroamylasemia screening. Macroamylasemia can occur in the presence of normal serum amylase, but the combination of hyperamylasemia with an amylase: creatinine renal clearance ratio of less than 1 percent is indirect but highly suggestive evidence of macroamylasemia. Abdominal pain has been anecdotally linked with macroamylasemia, but statistical correlation is lacking; thus, it is concluded that macroamylasemia is asymptomatic.

Assays

Macroamylase can be identified within 10 to 60 minutes using a dextran gel microcolumn for protein separation followed by incubation of the large-sized fractions with amylose and iodine to assay for amylase hydrolysis activity.[1] Fridhandler and Berk[69] have distinguished three types of macroamylasemia with this method: (1) Type 1 is characterized by serum hyperamylasemia and detection of amylase activity within the first ten minutes of incubation; (2) type 2 displays serum hyperamylasemia, but more than ten minutes of incubation is required for detection of amylase activity, and (3) type 3 displays normal serum amylase, and more than ten minutes of incubation is required. Among these three groups, type 1 has the highest level of total serum amylase activity, the highest ratio of macroamylase to normal-sized amylase in the serum, the highest amylase activity in the macroamylase-containing fractions, and the most diminished levels of urine amylase compared with type 2, which is intermediate, and type 3, which is last in these areas.

Multiple sera can be screened simultaneously for macroamylase using thin-layer gel filtration with the amylase substrate and iodine applied directly to the gel.[21,70] Unhydrolyzed starch takes up stain, and zones with amylase activity remain white. Normal serum generates a single white stripe, and macroamylasemic serum generates two white stripes. The microcolumn and thin-layer chromatographic techniques for detecting macroamylase have replaced standard columns in most laboratories because they are quicker, easier and less expensive to run. Berggren and Levitt[40] reported a macroamylase, however, that was not detectable by using the microcolumn, but was shown by isoelectric focusing and standard column chromatography. This "unusual" macroamylase was only marginally larger than normal serum amylase and may not have been resolvable with ultracentrifugation. Macroamylase is generally reliably identified by ultracentrifugation,[16] although this technique is time consuming.

Electrophoresis has been advocated as a screening test for macroamylasemia.[27,48] A proper matrix needs to be devised that will impede the migration of macroamylase while allowing passage of all isoamylases of varying charges, to make this assay specific. Isoelectric focusing distinguished an abnormal amylase from one patient that was eventually found to be macroamylase,[40] however, macroamylase complexes usually do not focus clearly.[54] Both of these techniques can confuse differences in charge with differences in size; even so, electrophoresis is a potentially useful screening method.

An indirect temperature-sensitive method for determining the presence of macroamylase is based on the increased enzyme activity of serum amylase at 45°C compared with 25°C. In sera of normal subjects and patients with pancreatitis,

the increase is fourfold, but in patients with macroamylasemia it can be up to eightfold.[71,72] This screening method successfully identified a case of macroamylasemia in a random sampling of 100 hospital inpatients.[32,73] If macroamylase represents only a small proportion of a patient's total amylase activity, this indirect assay might fail to detect it. Brohee and co-workers[36] could not detect a chromatography-proved macroamylase with this method. In the presence of unexplained hyperamylasemia, a pancreatic scan has been advocated by Mark and McCord[74] to provide, if the results are normal, indirect evidence of macroamylasemia. Such a technique may be useful in excluding pancreatitis,[75] but it is much too indirect to be useful in implicating macroamylasemia because there are many other nonpancreatic causes of hyperamylasemia[76,77] and more specific methods for diagnosing macroamylasemia.

Serum Amylase

An elevated level of serum amylase is insensitive and certainly not specific for diagnosing macroamylasemia.[76,77] Although the vast majority of cases have been identified during evaluation of hyperamylasemia, Barrows and colleagues[78] and Helfat and co-workers[79] together screened for macroamylasemia in 1,052 patients with a variety of disorders, who were chosen at random with respect to their serum amylase level. Of these, 16 patients with macroamylasemia were identified; however, the serum amylase level was elevated in only 2 and was within normal limits in the other 14.[69]

Amylase Clearance:Creatinine Clearance Ratio

An abnormally low renal amylase clearance: creatinine clearance (C_{AM}:C_{CR}) ratio has been advocated as a diagnostic screening test for macro-

TABLE 1.—*Reported Mean Values for C_{AM}:C_{CR} in Normal Subjects Assayed by Chromogenic, Saccharogenic and Iodometric Methods*

Investigators and Reference No.	*Year*	*No. of Subjects (total)*	*Mean C_{AM}:C_{CR} (percent)*	*Product (total)*
Chromogenic				
Blainey & Northam[5]	1967	9	3.02	27.18
Warshaw & Fuller[84]	1975	46	3.10	142.60
Long & Grider[85]	1976	20	1.30	26.00
Morton et al[86]	1976	24	1.24	29.76
Donaldson et al[87]	1977	25	2.60	65.00
Levitt et al[82]	1977	10	0.80	8.00
Marten et al[88]	1977	87	3.02	262.74
Murray & MacKay[89]	1977	40	1.50	60.00
Pasternack & Klockars[90]	1978	13	2.10	27.30
Hegarty et al[91]	1978	26	2.31	60.06
		(300)		(708.64)
Mean			2.36	
Saccharogenic				
Levitt et al[92]	1969	36	2.30	82.80
Levine et al[93]	1975	12	2.15	25.80
Warshaw & Lesser[94]	1975	46	3.10	142.60
Warshaw & Lee[95]	1976	25	3.00	75.00
Johnson et al[96]	1976	20	2.40	48.00
Morton et al[86]	1976	24	1.46	35.04
Levitt et al[82]	1977	10	2.19	21.90
Farrar & Calkins[97]	1978	69	3.04	209.76
		(242)		(640.90)
Mean			2.65	
Iodometric				
Mulhausen et al[98]	1969	11	3.62	39.60
Levitt et al[82]	1977	10	1.52	15.20
Schiffer et al[83]	1977	5	3.84	19.20
		(26)		(74.00)
Mean			2.85	

C_{AM}:C_{CR} = amylase clearance:creatinine clearance (ratio)

amylasemia.[80,81] In normal control subjects this ratio ranges from 0.80 percent[82] to 3.80 percent.[83] In addition, it has been suggested that the amylase assay method used can produce significant differences in the $C_{AM}:C_{CR}$ ratio.[82] There are three amylase assay methods in general use: chromogenic, saccharogenic and iodometric. Compiled data from surveys of normal control $C_{AM}:C_{CR}$ ratios are summarized in Table 1. The mean normal $C_{AM}:C_{CR}$ ratios for the three assays are as follows: chromogenic 2.36 percent, saccharogenic 2.65 percent and iodometric 2.85 percent. It is important to know the normal values for these assays because many reported macroamylasemic clearance ratios do not specify the assay method used or the associated control $C_{AM}:C_{CR}$ values.

The $C_{AM}:C_{CR}$ ratio is indeed significantly lower in macroamylasemic patients than in normal control subjects. In documented cases of macroamylasemia in which the clearance ratio was reported, it was less than 1 percent in 37 patients,* 1.01 percent in one patient[21] and greater than 1.01 percent in only four patients.[21,34,35,100] One of these four patients was a man with a posterior antral ulcer and back pain; the ratio in this patient ranged from 1.46 to 2.1 percent. The patient may have had superimposed mild pancreatitis, which can transiently raise the clearance ratio in a macroamylasemic person from less than 1 percent to 4.5 percent[40]; this patient was not retested later when he was asymptomatic. The other three of these four patients were screened together,[34,35,100] with 14 ratio determinations carried out. Only one was less than 1 percent; the other ratios were as high as 11 percent, with essentially the same spread as in a group of patients with acute pancreatitis. Control subjects were not tested, however, and no specific information was given on how the diagnoses were made.

An additional cautionary note about the sensitivity of the low clearance ratio is that it has only been applied to hyperamylasemic macroamylasemic patients. It may lack dependability in the absence of hyperamylasemia. Barrows and colleagues[78] and Helfat and co-workers[79] did not report clearance ratios in their screening studies that identified 14 normoamylasemic patients among the 16 cases of macroamylasemia found. At least 13 of the 16 patients had type 3 macroamylasemia,[69] which is usually associated with normal, rather than low, urinary levels of amylase. These patients might have had clearance ratios that overlapped with normal values. Nevertheless, except for four cases in which important data were lacking, the $C_{AM}:C_{CR}$ ratio has served as a sensitive indirect screen in patients with hyperamylasemia.

All patients reported in the literature with simultaneous hyperamylasemia and a low clearance ratio who have been so screened have had macroamylasemia except for five[48,101] who had salivary type (S type) hyperamylasemia with no detectable macroamylase. Two of the five had salivary gland enlargement and the other three had no obvious cause for this condition.

The mechanism for the decreased renal clearance of macroamylase is thought to be the large molecular weight of these complexes. They generally elute with the 100,000 or higher MW globulins on chromatograms and are too large for glomerular filtration. Proposed mechanisms for the low clearance ratio with salivary type hyperamylasemia include relatively slow renal clearance of the salivary compared with the pancreatic isoenzyme,[85,90,91,102,103] decreased nonrenal catabolism of the S-type isoamylase,[101] and the hypothetic presence of a macroamylase that dissociated during its analysis.[48]

Brohee and Delcourt[104] have mathematically illustrated the extent to which addition of a nonfiltered macroamylase decreases the clearance ratio of amylase to creatinine. This is shown in the following equation, which I have modified slightly.

In the presence of macroamylasemia, the renal clearance ratio is

$$\frac{C_{TA}}{C_{CR}} = \frac{C_A + C_M}{C_{CR}} = \frac{C_A}{C_{CR}} = \frac{\dfrac{U_{TA}}{P_{TA}}}{\dfrac{U_{CR}}{P_{CR}}} = \frac{\dfrac{U_A}{P_A + P_M}}{\dfrac{U_{CR}}{P_{CR}}}$$

multiplying by 1

$$\frac{\dfrac{U_A}{P_A + P_M}}{\dfrac{U_{CR}}{P_{CR}}} \times \frac{\left(\dfrac{P_A + P_M}{P_A}\right)}{\left(\dfrac{P_A + P_M}{P_A}\right)} = \frac{\dfrac{U_A}{P_A}}{\dfrac{U_{CR}}{P_{CR}} \times \left(1 + \dfrac{P_M}{P_A}\right)} = \frac{C_A}{C_{CR}} \times \frac{1}{\left(1 + \dfrac{P_M}{P_A}\right)}.$$

$$\therefore \frac{C_{TA}}{C_{CR}} = \frac{C_A}{C_{CR}} \times \frac{1}{\left(1 + \dfrac{P_M}{P_A}\right)},$$

where U = urine concentration, P = plasma concentration, C = clearance, $_A$ = amylase, $_M$ = mac-

*References 2, 3, 7-9, 21, 28-31, 36, 38, 40, 41, 48, 92, 99.

roamylase, $_{TA}$ = total amylase = $_M + _A$, $_{CR}$ = creatinine, $U_M = 0$, and $C_M = 0$.

From this equation it is apparent that as P_M increases $C_{AM}:C_{CR}$ decreases. The percentage of total serum amylase activity found within macroamylase has been measured at between 7 percent and 100 percent.[7,21,34,79,92] Using these values in the equation, one would expect to find urinary clearance ratios ranging from 93 percent down to 0 percent of normal. The actual observations of 0 percent to 40 percent of normal (assuming a normal ratio of 2.5 percent) probably relate to underestimation of the macroamylase component of total serum amylase activity. Levitt and coworkers[92] compared clearance ratios with the macroamylase component of total serum amylase activity in six patients and found a linear inverse relationship as the equation implies.

In the presence of hyperamylasemia, a $C_{AM}:C_{CR}$ ratio of less than 1 percent is thus a useful indirect screening method for macroamylasemia. Confirmation of the diagnosis, however, still requires a direct assay.

Clinical Characteristics

Abdominal pain was a presenting symptom in 37 patients with macroamylasemia,* although the cause of the pain often remained undiagnosed. This relationship may be biased because patients with abdominal pain are screened for hyperamylasemia more often than patients without this symptom; thus, more cases of hyperamylasemia are discovered among them. Macroamylasemia, as will be discussed in the next section, is more frequent in hyperamylasemic patients than in randomly selected subjects, so that any condition requiring amylase screening will seem to have an inordinately high frequency of simultaneous macroamylasemia. It has been suggested that macroamylase may be deposited in the pancreas and thus produce pain,[48] but there is no experimental evidence to support this hypothesis. The frequency of macroamylasemia among patients with and without abdominal pain has not been compared. No other symptom is associated with macroamylasemia, and until the aforementioned comparison is made, macroamylasemia cannot be considered to be symptomatic.

*References 14, 21-24, 32, 36, 39-41, 48, 67, 74, 99, 105.

Epidemiology

How common is macroamylasemia? This condition has been screened for in randomly selected patients irrespective of their serum amylase levels and in groups selected specifically for their normal or elevated serum amylase activities. Diagnostic methods have included microcolumn,[34,35,78,79,100] thin-layer chromatography,[21] temperature-activity ratio[72,73] and simultaneous presence of serum hyperamylasemia with $C_{AM}:C_{CR}$ ratio of less than 1 percent.[106] Although the last two methods are indirect and, thus, not absolutely conclusive in an individual patient, they are adequate for estimating frequency within a large population. The results of the surveys are summarized in Table 2. The frequency of macroamylasemia in randomly selected patients is 1.05 percent. Among people with normal serum amylase activities it is 0.98 percent, and among people with hyperamylasemia it is 2.56 percent.

Macroamylasemia occurs more often in males than in females. There are currently 194 cases of macroamylasemia reported in the worldwide literature.† The 195th case is described in this review. Of the cases, 99 were in males and 62 were in females; the sex was not reported in 33 cases. The relative frequencies according to sex

†References 2, 3, 7-10, 13, 14, 20-36, 39-41, 46-50, 55, 58, 61, 66, 67, 69, 72-74, 78, 79, 92, 99, 100, 105, 107.

TABLE 2.—*Frequency of Macroamylasemia*

Investigators and Reference No.	*Year*	*Method*	*Serum Amylase*		
			Random	*Normal*	*Increased*
Barrows et al[78]	1972	Microcolumn		9/868	1/23
Imrie & Henderson[73]	1972	Temperature ratio			0/39
Long & Kowlessar[21]	1972	Thin-layer column		0/55	3/51
Imrie et al[32]	1973	Temperature ratio	1/139		
Helfat et al[79]	1974	Microcolumn	7/612		1/10
Dreiling et al[106]	1974	Serum amylase, $C_{AM}:C_{CR}$	8/773		
Bindrich et al[34]	1976	Microcolumn			3/190
			16/1524	9/923	8/313
Total Frequency (percent)			1.05	0.98	2.56

$C_{AM}:C_{CR}$ = amylase clearance:creatinine clearance (ratio)

are 61 percent men and 39 percent women, a statistically significant difference ($P<0.005$). The preponderance in men is unexplained. Serum amylase is 16 percent higher in normal women than in normal men,[108,109] but perhaps frank hyperamylasemia occurs more frequently in men than in women, leading to more frequent macroamylase screening in men. Barrows and co-workers[78] and Helfat and colleagues[79] together screened a group of 1,052 patients with a variety of diseases. The group was equal in sex distribution and the patients had been selected irrespective of serum amylase levels. Of 16 patients with macroamylesemia, 15 were men.

Macroamylasemia is an acquired condition. The age at the time of discovery of the condition was reported along with the patient's sex in 98 of the 195 cases.* The average age at the time of diagnosis was 53.3 years in the 63 male patients reported and 49.6 years in the 35 female patients reported. The ages ranged from 8[67] to 77 years,[33,50] but most patients were in the fifth, sixth and seventh decades (Figure 1). Although neonates have a fully developed immunoglobulin production system,[110] macroamylasemia was not shown in umbilical cord blood from 200 newborn infants selected at random.[78]

Macroamylasemia occurs throughout the world. Racial distribution among American patients whose race was reported[9,10,20,21,39,74,99] included 22 whites, 8 blacks and 1 Native American. There are no reports of more than one case in the same family; 29 family members of four macroamylasemic patients were screened, but no additional cases were identified.[10,29,32]

The duration of macroamylasemia is variable, and its presence may reflect coexisting disease. Some patients had unexplained hyperamylasemia for over ten years before macroamylasemia was diagnosed[99]; presumably, this condition was present the entire time. Macroamylasemia has been documented to persist for at least 300 days[58] and 100 days[32] in two diabetic patients. Follow-up surveys of 19 patients known to have the condition, at least 17 of whom had chronic illnesses, showed persistence of macroamylasemia in all of four cases after a week or more,[79] in seven of nine after a month,[78] and in all of six after two to ten months.[21] Wilding and co-workers[2] described a woman in whom macroamylasemia was present for at least three months but disappeared a month before she died from chronic illness. Zeze and colleagues[33] described a woman whose macroamylasemia disappeared one month after choledocotomy. Hedger and Hardison[39] reported a case of transient macroamylasemia in a woman during a hospital stay for acute intermittent porphyria, but no time frame was reported. Thus, macroamylasemia can occur transiently during acute illness and chronically during prolonged illness, and may, therefore, represent a nonspecific response to disease. Additional cases followed for longer times will provide more information about the natural evolution of macroamylasemia.

*References 2, 3, 7, 8, 10, 14, 17, 20-33, 36, 39-41, 50, 58, 61, 67, 74, 79, 99, 105, 107.

Causes

Why does the body produce immunoglobulins or other substances that can bind serum amylase? Macroamylasemia has been reported with greater

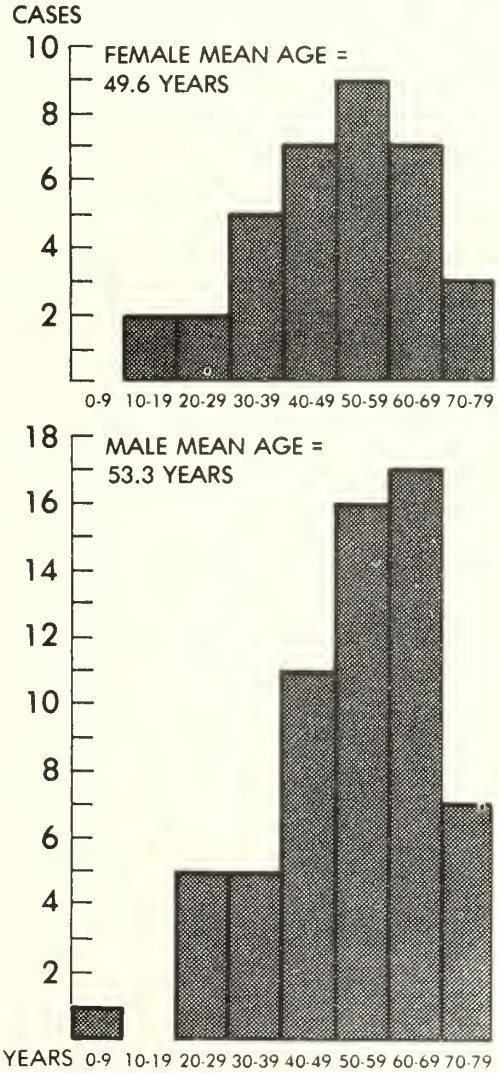

Figure 1.—Macroamylasemia—Age distribution by sex (including unpublished case).

frequency in patients in whom humoral immunity is disturbed, such as autoimmune diseases and cancer, or in patients in whom pancreatitis is a possible diagnosis, such as alcoholism, diabetes, cholelithiasis, malabsorption or pancreatitis itself. In the first setting, macroamylase appears to be a circulating complex of immunoglobulin and amylase, reflecting an aberrant state of immunoglobulin production. In the second setting there may be a spurious association because this group is generally screened for hyperamylasemia, whose presence also correlates with macroamylasemia. Macroamylasemia can also be iatrogenic.

Clinical Settings

The 108 patients with macroamylasemia whose clinical state has been described,* had isolated diseases of every organ system in the body; however, the following seven underlying disease states were found with some frequency.

Alcoholism. There were 19 cases of alcoholism coexisting with macroamylasemia.† In addition, seven patients with cirrhosis of the liver were reported although alcohol consumption was not mentioned.[32,33,35,50,61] Alcoholic patients are frequently screened for pancreatitis with serum amylase measurements and are occasionally found to have persistent unexplained hyperamylasemia that leads to macroamylase screening.

Pancreatitis. Eleven cases of acute or chronic pancreatitis with macroamylasemia were reported.[21,32,33,99] Close amylase surveillance in this group also leads to more frequent macroamylase screening, especially when hyperamylasemia persists out of proportion to the clinical condition.

Cancer. Eleven patients with macroamylasemia had cancer. The primary site was the lung in six cases,[35,50,79] the pancreas in two,[61] and the stomach,[50] esophagus,[50] and blood (leukemia)[48] in one each. Perhaps the tumors were associated with an abnormal antigen that cross-reacted with amylase.

Diabetes. Ten patients with diabetes,‡ including one with mumps-induced diabetic ketoacidosis,[58] had macroamylasemia. The factors that led to failure of the endocrine pancreas may also have subtly affected the exocrine pancreas leading to a mistaken recognition of amylase as a foreign substance stimulating production of amylase-binding immunoglobulin. In addition, diabetes can be a complication of pancreatitis, which is associated with macroamylasemia per se.

Cholelithiasis. Seven patients with cholelithiasis and macroamylasemia have been reported.[21,24,33,40,107] In addition, a 73-year-old Asian man with hyperamylasemia, cholelithiasis, a $C_{AM}:C_{CR}$ ratio of 0.2 percent and macroamylasemia confirmed by microcolumn chomatography§ was seen at the University of California, San Francisco (Klonoff, unpublished observations). Most cholelithiasis workups include measurement of serum amylase, which can lead to discovery of inappropriate hyperamylasemia, and subsequent macroamylase screening.

Autoimmune Disorders. The first patient discovered to have macroamylasemia[2] died of a connective tissue disease characterized by fever, facial rash, phlebitis, leg ulcers and positive lupus erythematosus preparations. Six subsequent cases of autoimmune disorders associated with macroamylasemia have included systemic lupus erythematosus,[99] rheumatoid arthritis,[24] ankylosing spondylitis,[20] cryoglobulinemia,[41] monoclonal gammopathy[8] and heroin abuse.[79] The heroin addict, who also had bacterial endocarditis, had abnormal results of serology tests: positive latex fixation, and HBAg, and decreased serum complement. As mentioned earlier, a patient receiving hog pancreatic enzyme supplements for malabsorption had a macroamylase containing IgA with higher affinity for hog amylase than human amylase.[38] He may have become sensitized to hog amylase and produced antibodies to it that cross-reacted with human amylase. It is not surprising that macroamylasemia should be associated with disease states in which there are circulating immunoglobulins directed against a patient's own antigens.

Malabsorption. Four of the first ten macroamylasemic patients identified had a syndrome of malabsorption, atrophy of intestinal villi and macroamylasemia.[2,7,8,45] The presence of a small quantity of macroamylase, an IgA-amylase complex,[7] in the intestinal fluid of one of them led to speculation that the complex might be formed in the intestine from luminal IgA and amylase and that it might be cytotoxic and lead to atrophy of the villi. Only three additional macroamylasemic patients with

*References 2, 7, 8, 10, 14, 17, 20-26, 29, 32, 33, 35, 36, 39-41, 46, 48, 50, 55, 58, 61, 67, 74, 79, 99, 105, 107.

†References 10, 17, 21, 26, 32, 35, 36, 74, 79, 99.

‡References 17, 24, 32, 55, 58, 61, 79, 107.

§Kindly performed by J. Edward Berk, MD, Department of Medicine, University of California, Irvine.

malabsorption were reported subsequently,[22,40,99] and thus interest in this syndrome has waned.

The occurrence of macroamylasemia in these seven disease states may well reflect causes or effects of this condition. However, such relationships are speculative and are even less likely to be present for disease states with fewer reported cases. For example, after identifying macroamylasemia in a patient with a head injury, Imrie and co-workers[32] screened the next 20 neurosurgical admissions and failed to discover another case.

Iatrogenic Macroamylasemia

Infusion of hydroxyethyl starch (HES), but not dextran or gelatin, has produced serum macroamylasemia[37,42-44] with formation of an HES-amylase complex. No changes in serum levels of lipase, aspartate aminotransferase (formerly serum glutamic oxaloacetic transaminase), lactate dehydrogenase (LD), alkaline phosphatase, or gamma glutamyl transferase were noted. Serum amylase levels generally returned to the normal range within 72 hours in patients whose C_{CR} exceeded 10 ml per minute,[42-44] but in one patient[37] macroamylasemia persisted for four days.

Clinical Significance

The discovery of macromolecular amylase in 1964[2] established an additional cause of hyperamylasemia, but simultaneously raised several questions about the clinical significance of macroamylasemia. Who should be evaluated for macroamylasemia? What does it mean for a patient to have this condition? What should be done if macroamylasemia is diagnosed?

Any patient with asymptomatic hyperamylasemia and normal renal function (an important route of amylase elimination) should be evaluated for macroamylasemia. Detection of such cases most commonly occurs during automated screening of multiple chemistry values from a single blood specimen or during follow-up tests after clinical resolution of pancreatic or parotid disease. Because most hospital laboratories do not assay for macroamylase at present, the simplest confirmatory screening method (as mentioned earlier) is simultaneous determination of serum amylase and $C_{AM}:C_{CR}$ ratio. Identification of macroamylase can short circuit an otherwise prolonged and expensive workup for hyperamylasemia.

Macroamylasemia occurs with a variety of diseases but with apparently increased frequency in states of altered immunity such as autoimmune diseases and cancer. The occurrence of macroamylasemia in apparently healthy persons as well suggests that it may be an early sign of disease, either as a marker for particular groups of diseases or as a nonspecific disease-induced dysproteinemia with amylase-binding capability. This possibility is reinforced by the correlation in some patients between the appearance or disappearance of macroamylasemia and the extent of coexisting disease. Whether the presence of macroamylasemia predicts any of these conditions, or its disappearance predicts recovery[33,39] or death[2] is not known. Long-term follow-up of apparently healthy macroamylasemic persons is needed to see whether a particular disease develops or not. A macroamylase assay might someday serve as a screening test for diseases of altered immunity.

Macroamylasemia is a benign condition that does not require treatment. When macroamylasemia accompanies systemic disease, it is a byproduct of the disease state and all treatment should be directed at the underlying problem. Although macroamylase has been found in the duodenal aspirate of one patient with atrophy of intestinal villi and malabsorption,[7] causal relationship was found. It has been speculated but not documented that macroamylasemia causes abdominal pain.[48] If macroamylase were independently cytotoxic, one might expect it to bind complement; however, its complement-binding potential has not yet been tested. A patient with the triad of unexplained abdominal pain, hyperamylasemia and macroamylasemia is often subjected to exploratory laparotomy for examination of the pancreas. This is nonproductive and should be avoided. Fifteen patients with this triad were subjected to laparotomy[9,21,32,74,99] and no abnormality of the pancreas was found in 13, although no biopsies were obtained. The 2 patients with a visibly abnormal pancreas were the only patients among the 15 with clinical pancreatitis, acute in one case[21] and chronic in the other.[99] Thus, laparotomy showed no gross pancreatic pathology in all hyperamylasemic patients who had macroamylasemia without clinical pancreatitis. If macroamylasemia is found to be a harbinger of eventual development of systemic disease, then the approach to the macroamylasemic patient will have to include appropriate follow-up and screening for the associated disease. Without confirmation

of such an association, macroamylasemia should be regarded as a benign condition that requires no special management or treatment.

Other Immunoglobulin-Complexed Enzyme Disorders

To the extent that macroamylase represents a phenomenon in which immunoglobulin is complexed with a circulating enzyme (amylase), it is not unique. Lactate dehydrogenase, alkaline phosphatase, creatine kinase (formerly creatine phosphokinase), alanine aminotransferase (formerly serum glutamic pyruvic transferase) and glucose-6-phosphate dehydrogenase have also been found complexed with immunoglobulin. A designation of this phenomenon as an immunoglobulin-complexed enzyme (ICE) disorder is suggested. Each of the ICE disorders represents a possible cause for an unexplained elevated level of a serum enzyme. Immunoglobulin-complexed nonenzymatic proteins have also been reported. The ICE disorders represent an incompletely understood dysproteinemic response of the human immune system to a variety of disease states.

MacroLDemia

An isolated elevated serum LD level in a healthy person is often dismissed as "nonspecific." The patient is less likely to undergo an extensive workup if he has elevated LD activity than if he has elevated amylase activity because there are so many more causes for the former, and each diagnostic test is likely to have a low yield. The presence of macromolecular LD is yet another cause of elevated serum LD levels.

After amylase, LD is the next most common enzyme found in an immunoglobulin-complexed state. The presence of a circulating macromolecular LD is analogous to that of macromolecular amylase, which is designated as macroamylasemia. Similarly, macromolecular LD can be designated as "macroLD" and the presence of circulating macroLD as "macroLDemia." This condition does not appear to cause or be associated with any symptoms or particular diseases. Its clinical significance, like that of all the ICE disorders, appears to lie in its tendency to be an often overlooked cause of an elevated serum enzyme level, in this case LD. MacroLDemia, however, is associated with the presence of antinuclear antibodies and, therefore, indirectly with autoimmune disease.

The physical properties of macroLD are heterogeneous. Lactate dehydrogenase is a tetramer of two types of subunits, H and M, and can be separated electrophoretically into five isoenzymes (H_4, H_3M, H_2M_2, HM_3 and M_4). Each subunit has an MW of 34,000 and each isoenzyme has an MW of 134,000.[111] Forty-five patients with the abnormal macromolecular form of LD have been identified.[112-126] MacroLD was discovered during analysis of sera from patients with persistently elevated serum LD activity. The macroLD differs from all normal LD isoenzymes in its chromatographic, electrophoretic and kinetic properties. Whereas normal LD elutes from Sephadex G-200 gel between albumin and gamma globulins, in 42 patients LD activity eluted early, between the macroglobulins and gamma globulins, in addition to* or instead of[114,115,119,122,126] normal LD. Two macroLD complexes dissociated to normal size during gel filtration[119] and one was not tested.[120] The MW of the macroLD has been estimated at 200,000 to 400,000.[115,125,126] Electrophoresis of the macroLD showed pronounced heterogeneity among the patients. In each case there was at least one extra abnormal band, as well as a deficiency of one or more of the normal LD isoenzymes. Abnormal large MW fractions on the chromatogram contained the abnormal LD fractions seen with electrophoresis. The physical properties of the macroLD complex are heterogeneous but differ from normal LD and usually each other in their heat stability† and their responses to nicotinamide adenine dinucleotide,[116,118,119,123] mercaptoethanol,[118,119] $(NH_4)_2SO_4$,[120] pyruvate[125] and urea.[125]

MacroLD contains immunoglobulin complexed to LD in most cases studied (Table 3). Among the 45 cases identified, immunoelectrophoresis detected 24 cases of IgA linked to LD,[114,116-118,120-122] 16 cases of IgG linked to LD[115,119,123,125] (14 of these were of the subclass IgG_3 and two were not subclassified), and one case of both IgG_1 and IgA linked to LD.[123] Both kappa and lambda light chains have been noted either alone or together in the same patient.[119-123,127] Hemagglutination inhibition may be a more sensitive assay than immunoelectrophoresis or light chain analysis.[127]

*References 112, 113, 116-118, 121-125.
†References 112, 116, 118, 119, 123-125.

Although theoretically immunoglobulins directed against an LD isoenzyme that contains both subunits might precipitate all five isoenzymes containing one or both of these subunits, antibodies directed exclusively against one hybrid isoenzyme have been observed.[122,128] Further studies are needed to locate the immunoglobulin's site of binding to LD and to explain how a single hybrid isoenzyme can be bound selectively.

Elevated immunoglobulin levels may contribute to formation of macroLD but are not essential. Quantitative immunoglobulins were measured in 11 patients with IgA-LD complexes and IgA was elevated in five of them.[114,118,120,121] They were also measured in six patients with IgG-LD complexes and IgG was elevated in four of them.[115,119,123,125]

MacroLD is an acquired disorder. The abnormal properties of macroLD are due to interaction with some substance in the serum, rather than to a genetically abnormal structure. This conclusion is based on four observations: (1) The LD from erythrocytes, leukocytes, and lymph node extract is normal in patients with macroLD in the serum,[113,116-121,123] although salivary IgA-LD complexes were found in one of two patients screened.[118,121] (2) Serum specimens from these patients mixed with normal human serum[114-120,122-126] or horse, cow, hog or rabbit serum[122] reproduces the electrophoretically abnormal LD rather than producing two LD families. (3) The serum LD abnormality can be transient.[118-120,123,124,126] (4) Abnormal circulating LD has not been detected among family members of affected patients.*

Establishing the diagnosis of macroLDemia requires chromatographic or immunologic evidence of an abnormal LD complex. Ultracentrifugation has not been used to study macroLD but would be a definitive diagnostic method. An elevated serum LD level is not specific for diagnosing macroLDemia, and is also insensitive because 5 of the 45 patients with macroLDemia had normal levels of LD.

The frequency of an electrophoretically abnormal LD has been estimated as one in 2,500[113] and five in several thousand.[129] The frequency of an immunoglobulin-complexed LD has been estimated at less than one in 10,000.[118] Biewenga and Feltkamp[123] screened sera from 100 patients with rheumatoid arthritis and identified a single case of macroLDemia, but found no cases among 19 patients with systemic lupus erythematosus. Twenty-two cases each have occurred in men and women; the sex of another patient was not disclosed. The mean age at the time of diagnosis was 58.7 years, and the age distribution was bimodal, with a small peak in the third decade and a large peak in the seventh decade (Figure 2). No particular disease state is associated with macroLDemia, but in 13 of the 45 patients antinuclear antibody studies were positive, suggesting an association with systemic autoimmune disease.

Circulating LD can thus be found in a macro-

*References 112, 113, 116, 118, 121, 126.

TABLE 3.—*Cases of MacroLDemia*

Investigators and Reference No.	*Year*	*Previously Unreported Patients*	*Molecular Weight*			*Immunoglobulin-LD Complexes*					*Elevated Serum LD*	*Positive ANA*
			Elevated	*Normal*	*Untested*	*IgA*	*IgG*	*IgA+IgG*	*Absent*	*Untested*		
Lundh[112]	1967	1	1	..	..	..	..	..	1	..	1	..
Voigt[113]	1967	1	1	..	..	..	..	..	..	1	1	..
Ganrot[114]	1967	1	1	..	..	1	..	..	..	..	1	1
Kindmark[115]	1967	1	1	..	..	..	1	..	..	..	1	1
Biewenga & Thijs[116]	1970	1	1	..	..	1	..	..	..	..	1	..
Nagamine[117]	1972	2	2	..	..	2	..	..	..	..	2	..
Biewenga[118]	1972	7	7	..	..	7	..	..	..	..	7	..
Biewenga[119]	1973	3	1	2	..	..	3	..	..	..	3	2
Markel & Janich[120]	1974	1	..	..	1	1	..	..	..	..	1	..
Thomas et al[121]	1974	1	1	..	..	1	..	..	..	..	1	..
Biewenga & Feltkamp[122]	1975	11	11	..	..	11	..	..	..	..	9	2
Biewenga & Feltkamp[123]	1975	12	12	..	..	..	11	1	..	..	10	7
Tanaka et al[124]	1976	1	1	..	..	..	..	..	1	..	1	..
Hayashi et al[125]	1976	1	1	..	..	..	1	..	..	..	1	..
Meaney et al[126]	1976	1	1	..	..	..	..	..	1	..	..	..
TOTALS		45	42	2	1	24	16	1	3	1	40	13

ANA = antinuclear antibody, LD = lactate dehydrogenase

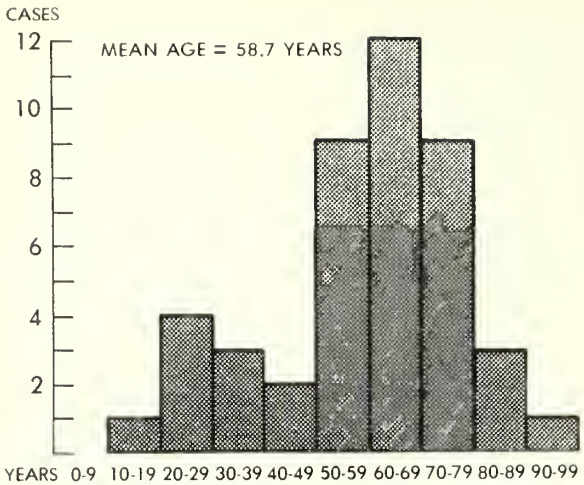

Figure 2.—MacroLDemia—Age distribution.

molecular form that is usually complexed with an immunoglobulin and has heterogeneous physical properties; this form can be designated as macroLD. The presence of macroLD or macroLDemia appears to have clinical significance similar to that of macroamylasemia.

Other Enzymes

Serum enzymes other than amylase and LD have been found linked to immunoglobulins. Four patients with circulating IgG-alkaline phosphatase complexes have been reported.[130,131] The IgG light chains were lambda in all four. The bound alkaline phosphatase was hepatic in two cases, osseous in one, and both hepatic and osseous in one. Human intestinal and placental as well as other mammalian alkaline phosphate isoenzymes were not bound by the patients' sera. Three of the patients had an elevated serum level of alkaline phosphatase and two had osteoporosis. The frequency of this disorder is estimated to be 0.1 percent of patients with an elevated serum level of alkaline phosphatase.[131] Urdal and Landaas[132] reported six patients with macromolecular complexes of the creatine kinase (CK) BB isoenzyme, or macroCK. In four cases the complex contained IgG, and in two no immunoglobulin could be demonstrated. The patients had no clinical disorder in common. An incidence of five cases of circulating macroCK among 310 randomly screened sera specimens was reported, and three of the five were due to IgG-CK complexes. It is noteworthy that immunoglobulin-bound CK-BB can be measured as MB in an ion exchange column chromatography assay, leading to a possible misdiagnosis of myocardial infarction. Kajita and co-workers[133] screened 500 patients with chronic liver disease and found a circulating IgG-alanine aminotransferase complex in 16 of them. Fifteen of the 16 had an elevated serum level of alanine aminotransferase. In a report by Eng[134] there were five patients with electrophoretically abnormal glucose-6-phosphate dehydrogenase that was bound to an uncharacterized substance in the serum. One of the patients had cancer of the penis, one had hemolytic anemia and one had fever of obscure origin; two were screened from among 131 apparently healthy volunteers.

Nonenzyme Proteins

The protease inhibitor α_1-antitrypsin has been reported to be complexed with IgA in patients with IgA myeloma, although the serum level of this protein was not reported in any of the cases and therefore it is not known if the level was elevated.[135-137] Complexes of IgA and α_1-antitrypsin may constitute 1 percent of plasma IgA.[136] Immunoglobulins complexed with a variety of other nonenzymatic proteins have also been reported, including albumin[64,138-142] and haptoglobin.[138] Rheumatoid factor[143] and mixed cryoglobulins[144] can be considered as immunoglobulin-complexed immunoglobulins. Immunoglobulins have spontaneously developed against multiple coagulation factors[145] and peptide hormones, such as insulin,[146-148] glucagon[149] and human chorionic gonadotropin-luteinizing hormone,[150] in nonsensitized patients.

Conclusions

The ICE disorders represent a small but growing group of phenomena in which an immunoglobulin is complexed with a circulating serum enzyme or nonenzyme protein to create a macromolecular complex. Macroamylasemia is the most extensively studied member of the group. If the factors leading to synthesis of ICE immunoglobulins could be modified to produce immunoglobulins specifically directed against antigens of tumors or infectious agents instead, then the lessons learned from ICE disorders could help treat numerous diseases.

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Specialty Conference

Discussants

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This is an edited transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor-UCLA Medical Center, Torrance, California. This transcript has been edited by Thomas T. Yoshikawa, MD and Lucien B. Guze, MD.

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Salmonellosis

THOMAS T. YOSHIKAWA, MD:* Salmonellosis, or infections caused by salmonellae, remains an important disease in the United States. In 1978 and 1979 more than 29,000 isolates of salmonellae from humans were reported to the Center for Disease Control.[1,2] Although salmonellosis is clinically associated with underdeveloped countries, lower socioeconomic populations, poor hygiene, and contaminated food and water, physicians must still be aware of this infection, even in our modern society. With international tourism a common activity, physicians should consider that *Salmonella* infections may be acquired outside the United States.[3] Studies have indicated that at least 33 percent of typhoid fever cases in the United States are acquired during travels outside the states.[4]

A review of salmonellosis would be useful for practicing physicians. This discussion will be divided into (1) a brief history of salmonellosis, (2) microbiology, epidemiology and pathogenesis of salmonellosis, (3) clinical spectrum and management of salmonellosis and (4) precautions and recommendations for travel.

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Historical Aspects of Salmonellosis

PAMELA HERBERT, MD†

TYPHOID FEVER has probably been prevalent since the age of Hippocrates, but the first clear description is that of Thomas Willis of Wiltshire, England, in 1659.[5] In modern times it has caused frequent epidemics in army camps and in crowded cities. No respecter of classes, it attacks rich and poor alike through the medium of contaminated water and food. Albert, Prince Consort of Queen Victoria, died of typhoid fever in 1861 at the age of 42.[6]

John Huxham of Devon, writing in 1739, distinguished two kinds of enteric fevers: putrid malignant (typhus) and slow nervous (typhoid).[7] French physicians in the first third of the 19th century described swelling and ulceration of Peyer patches and enlargement of mesenteric lymph nodes in patients dying of what Prost called in 1804 "mucous fever." In 1813 mucous fever was identified by Petit and Serres as the condition Huxham had described as slow nervous fever.[8]

It was a Frenchman, Pierre Bretonneau of Tours, who recognized that slow nervous fever was a distinct clinical entity caused by a specific, albeit unknown, agent. Until this time it was still

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considered possible that all fevers were one disease with symptoms and signs varying from patient to patient depending on the circumstances of the illness. Bretonneau showed that the pathological findings in slow nervous fever were unique, differentiating it from all other fevers, including typhus, in which lesions of Peyer patches were not found.[6,8] He was convinced that the disease was contagious and proposed a new name for it, dothienenteritis (Greek *dothien:* circumscribed skin lesion).[8]

This unwieldy name was superseded by the term "fièvre typhoïde" (resembling typhus), introduced by Pierre Louis in his famous and comprehensive book on the disease published in 1829.[7] The word typhus derives from a Greek combining form meaning stupor and had been used in connection with enteric fever since its introduction by de Sauvages in 1759.[9]

Typhus and typhoid continued to be confused, however, until William Gerhard of Philadelphia in 1837 and the English physician Sir William Jenner in 1849 each wrote eloquent monographs separating the two diseases.[7] Jenner spoke from personal experience; during the course of his researches, he had contracted both maladies.[8]

Studies of epidemics by Piedvache in France in 1849 and by Murchison in England in 1858 showed that typhoid fever was a contagious disease. Murchison thought that it arose from a nonspecific corruption of air and water that, once the disease was contracted, could be further spread by intake of air, water or food that had been in contact with a person ill with the fever.[7] The Englishman William Budd of Devon made a careful study of an outbreak in Cowbridge in 1853. Rejecting the spontaneous generation theory, he thought that typhoid was due to a "self-propagating" principle and that all cases arose from antecedent cases. He realized that "the contagious element by which it is mainly propagated is contained in the specific discharges from the diseased intestine." He added, "The sewer . . . is, so to speak, the direct continuation of the diseased intestine."[10]

In 1880 C. J. Eberth saw typhoid bacilli in sections of lymph nodes and spleen from patients dying of typhoid fever.[8] Georg Gaffky, a Prussian army surgeon, grew the organism in pure cultures in 1884.[5] Durham, Pfeiffer and Kolle in 1896 used a prepared antiserum to identify the organisms by specific agglutination and immobilization, and Fernand Widal in 1896 showed the agglutinating reaction of serum from typhoid patients for the Eberth bacillus.[8]

The first practical typhoid vaccine was prepared from heat-killed bacteria by Sir Almroth Wright and was used to inoculate more than 3,000 soldiers in India in 1898. The admission rate there for typhoid fever dropped from 8.9 to 2.3 cases per 1,000, and there were fewer fatalities among these men, who nevertheless contracted the disease despite previous vaccination.[8]

Paratyphoid fever was first described by Achard and Bensaude in 1896. A severe outbreak occurred among British troops immunized against typhoid fever on the Gallipoli peninsula in 1915. Subsequent vaccines were fortified with *Salmonella paratyphi* A and B.[8]

Even before the development of specific vaccines, typhoid fever had begun to yield to improvements in sanitation. Following the passage of the Public Health Act in 1875 in Great Britain, the death rate from typhoid fever declined more than 50 percent during the next decade.[6]

The present name for the genus *Salmonella* was proposed by Lignières in 1900, for D. E. Salmon, who with Theobald Smith first isolated *Salmonella cholerae-suis*. This nomenclature was officially adopted in 1933.[11] Studies by White (1925) and Kauffman (1930) led to the Kauffman-White serological classification of salmonellae. Finally, the more contemporary work by Woodward and Hook provided a greater understanding of the pathogenesis and treatment of salmonellosis.[11]

Microbiology, Epidemiology and Pathogenesis of Salmonellosis

PHYLLIS A. OILL, MD*

Microbiology

Salmonella ORGANISMS are members of the family Enterobacteriaceae. They are nonspore-forming, aerobic, facultatively anaerobic, Gram-negative bacilli. *Salmonella* are motile by peritrichous flagella. Like that of all other enterobacteria, the cell wall of *Salmonella* is a complex structure composed of lipids, polysaccharides, protein and lipoproteins.[12] Endotoxin is the lipopolysaccharide portion of the cell wall (although some protein may also be present), with lipid A (lipid moiety

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of endotoxin) being responsible for the biological effects.[13] The common core monosaccharides and polysaccharides of endotoxin are also called somatic O antigens.[12] For *Salmonella* there are approximately 60 O antigens, which are designated by numbers. Additionally, there are several different flagella (H) antigens that are identified by numbers and letters. Based on a strongly reacting somatic antigen (major determinant) and one or more minor somatic antigens, salmonellae may be separated into major groups using specific antisera. Using the Kauffman-White schema, most salmonellae that cause human disease belong to groups A, B, C_1, C_2, D and E.[14] For specific serotype identification, the flagella antigens must be identified. Some serotypes of *Salmonella*—for example, *S typhi*—possess a capsular antigen called the virulence (Vi) antigen, which envelops the cell wall.

Using somatic and flagella agglutination reactions, more than 2,200 serotypes have been identified.[15] Previously, salmonellae were named according to the disease and animal from which they were isolated—such as *S cholerae-suis*. Later, the nomenclature was changed so the organisms got their names from the town, country or region in which they were first isolated—for example, *S saint-paul*. Traditionally, the various *Salmonella* serotypes have been treated as species (such as *S typhimurium*) and this practice is still common in the medical literature. However, Ewing has proposed only three primary species: *S typhi* (one serotype) and *S cholerae-suis* (one serotype), with *S enteritidis* encompassing all the remaining serotypes.[16] Hence, *S typhimurium* is designated *S enteritidis*, serotype Typhimurium. This latter nomenclatural approach is slowly being adopted by more and more microbiologists and infectious disease specialists.

Salmonella grow readily on most media including blood agar, MacConkey agar or eosin-methylene blue. Cultures of body fluids that are normally sterile (joint fluid, cerebrospinal fluid) can be grown on these media. However, with specimens such as feces, which contain many other organisms, highly selective media such as bismuth sulfate agar or desoxycholate agar should be used. The isolation of an aerobic Gram-negative bacillus that ferments glucose and mannose but not lactose or sucrose should alert the clinician that the laboratory is possibly dealing with a *Salmonella* isolate. *Salmonella* can readily be identified in most clinical laboratories by a variety of chemical tests. Moreover, a presumptive identification of *S typhi* and nontyphi *Salmonella* can be made by simple biochemical reactions. Gas production from glucose, ornithine reaction and rhamnose reaction are negative for *S typhi*, but are all positive for nontyphi *Salmonella*.

TABLE 1.—*The Ten Serotypes of* Salmonella *Most Frequently Isolated From Human Sources in the United States in 1978-1979**

Serotype	Number of Isolates	Percent of Total	Rank in 1979/1978
typhimurium	10,153	32.6	1/1
enteritidis	2,633	8.5	2/3
heidelberg	2,490	8.0	3/2
newport	1,915	6.2	4/4
infantis	1,417	4.5	5/5
agona	1,103	3.5	6/6
saint-paul	856	2.8	7/9
typhi	647	2.1	8/8
montevideo	613	2.0	9/7
oranienburg	592	1.9	10/..
Subtotal	22,419	72.1	
Others	7,994	27.9	
TOTAL (all serotypes)	31,123	100.0	

*Adapted from the Center for Disease Control.[1,2]

Epidemiology

Salmonella infections occur worldwide. As mentioned in the opening remarks, salmonellosis is not uncommon in the United States. Although approximately 25,000 to 30,000 cases of salmonellosis are reported each year from the United States, these probably represent only 1 percent of the true incidence.[17] However, the incidence of *S typhi* infections appears to be declining.

Enteric fever caused by *S typhi* (typhoid fever) is acquired by ingesting the organism via contaminated food or drink. In contrast to the transmission pathway of other salmonellae, humans are the only true reservoir for *S typhi*. Hence, outbreaks of *S typhi* can usually be traced back to food or drink that has been contaminated by another infected person who is excreting the organism, usually in the feces. Occasionally, insects or flies have been implicated in carrying organisms from feces to food or drinks. In countries or areas of the United States where pure water supplies are scarce, and effective sewage disposal or other sanitation measures are suboptimal, the incidence of typhoid fever is high. The attack rate of *S typhi* is equal among males and females, but is slightly greater in children than in adults. There appears to be no seasonal variation for cases in the United States.[4] A chronic

biliary carrier state occurs more frequently in women than men, perhaps because older women have a higher prevalance of gallbladder disease.

Salmonellosis caused by *Salmonella* serotypes other than *S typhi* ("nontyphi" salmonellosis) are most frequently isolated from both human and nonhuman sources.[17] The ten most frequently isolated serotypes of *Salmonella* from humans in the United States in 1978 and 1979 are shown in Table 1.[2] Nontyphi salmonellae are primarily pathogens of animals, both warm- and cold-blooded species. *Salmonella* organisms have been isolated from virtually all animal species including chickens, turkeys, ducks, cows, pigs, sheep, seals, donkeys, dogs, cats, turtles, guinea pigs, lizards and snakes.[18] Human acquisition of nontyphi salmonellosis occurs from ingestion of contaminated poultry, poultry products, meats (beef or pork), dairy products and, less frequently, water. Animal infections can occur by animal-to-animal transmission or by ingestion of contaminated animal foods.

Nontyphi *Salmonella* infections occur with the greatest frequency during warm weather periods; in the United States, this is between July and November.[19] Children under the age of 5 years, particularly those in the first year of life, have the highest attack rate of salmonellosis. Although the largest number of outbreaks occur in the home environment, institutional outbreaks of salmonellosis are very common. Most institutional cases occur in acute care hospitals, pediatric wards and nurseries, followed in number of occurrences by nursing homes, psychiatric hospitals and institutions for the retarded.[20] Whereas contaminated food or drink is responsible for most outbreaks associated with restaurants, banquets, food stores and schools,[21] nosocomial outbreaks have not only been attributed to food or drink but also to blood products,[22] pharmacologic and diagnostic preparations derived from animals (for example, bile salts, carmine dye, liver extract, pepsin and thyroid extracts) and cross-infection.[20] Cross-infection occurs by person-to-person transmission[23,24] or by contact with contaminated fomites or diagnostic equipment.[25]

Pathogenesis

Several factors (inoculum, serotype and host) appear to play important roles in the development of disease following ingestion of *Salmonella* organisms. McCullough and co-workers[26,27] reported that a large quantity of organisms (10^6) was required in order to produce disease consistently in human volunteers. These findings were again confirmed by Hornick and associates.[28] In their investigations they showed that oral inocula of a strain of *S typhi* in quantities of 10^5, 10^7 and 10^9 produced disease in 28 percent, 50 percent and 95 percent of the volunteers, respectively.

The serotype of *Salmonella* may determine the clinical syndrome produced. Although *S typhi* is the classic serotype causing enteric fever (typhoid fever), other serotypes can cause this syndrome too (called paratyphoid fever). Gastroenteritis is most commonly caused by *S typhimurium*.[29] *Salmonella cholerae-suis* regularly invades the bloodstream producing bacteremic syndromes (but not enteric fever) and localized infections, especially in vascular structures.[29] *Salmonella* mycotic aneurysm and endocarditis are most commonly associated with *S cholerae-suis*.[30,31] *Salmonella typhimurium* and *S derby* appear to be most commonly isolated from patients with salmonellosis and neoplastic disease.[32,33]

Several host factors appear to be important in

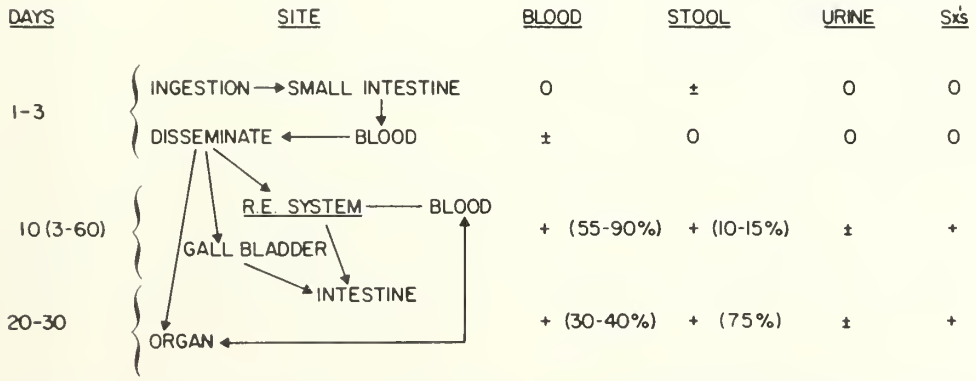

Figure 1.—Enteric fever: positive culture sites correlated with pathogenesis. R.E. = reticuloendothelial; Sx's = symptoms.

the acquisition of salmonellosis. Local gastrointestinal factors such as gastric acidity appear to influence the number of viable organisms; low pH will kill *Salmonella* organisms. Diseases of the stomach (or gastrectomy) that either decrease gastric acidity or enhance gastric emptying have been associated with *Salmonella* enteritis.[34,35] Alteration of the normal intestinal flora by administration of antibiotics may cause infection to occur with a small inoculum or possibly prolong the fecal shedding of nontyphi salmonellae.[36,37] As mentioned earlier, age is an important factor in the epidemiology of salmonellosis. The majority of nontyphi *Salmonella* infections occur in children younger than 5 years, particularly under the age of 1 year.[1,38] The specific mechanism for this age predisposition is not known although several factors could be operative, such as high frequency of fecal-oral contamination, decreased antibacterial activity of the normal intestinal microflora or immaturity of the immune systems.

Certainly, it appears that alteration of the cellular or humoral immune system, or both, may be important for predisposing to salmonellosis because several reports have shown the association of salmonellosis and malignancy.[32,33,39] Whether the underlying malignant conditions or the associated chemotherapy, radiotherapy, surgical treatment and hemolysis are the risk factors is not clear. Hemolysis is particularly important because sickle hemoglobinopathies, malaria and bartonellosis are associated with increased incidence of *Salmonella* infections.[18] Postulated mechanisms for hemolytic predisposition are defects in complement function, impairment of phagocytosis and abnormalities in killing of *Salmonella* following erythrophagocytosis, autosplenectomy or alteration in the immune system. Presence of *Schistosoma* infection leads to an increased incidence of *Salmonella* infection.[40] The *Salmonella* apparently localizes in the integument of a mature *Schistosoma* worm.[41] Elimination of schistosomiasis will eradicate the *Salmonella* infection.[18] Finally, the presence of chronic gallbladder disease, particularly cholelithiasis, favors the development of a chronic *Salmonella* carrier state, with persistent biliary excretion of the organism.

Development of salmonellosis occurs following ingestion of the organism. Viable bacteria pass to the small intestine where they multiply. Following multiplication, an infected individual may be totally asymptomatic and transiently shed the organisms in the feces. The pathogen then can disseminate hematogenously to the reticuloendothelial system, gallbladder or other organ sites. At these sites, the salmonellae may further replicate. From the reticuloendothelial sites, secondary bacteremia may occur causing an enteric fever syndrome, or organisms may again invade the small intestine. Gallbladder involvement leads to organisms localized to the intestinal tract via bile excretion. If salmonellae localize to an organ site (such as bone, meninges or heart), suppuration with secondary bacteremia may occur. These pathogenetic pathways are typical for enteric fever and are summarized on the left side of Figure 1. Alternatively, after intestinal multiplication, active infection may develop resulting in symptomatic acute *Salmonella* enterocolitis. Localization of the disease to the intestinal tract is usual; however, secondary bacteremia may occur with a clinical picture of Gram-negative sepsis, particularly in the immunocompromised host (malignancy group).

The clinical manifestations of enteric fever, primarily the pyrexia and toxemia, have been traditionally ascribed to continuous endotoxemia.[42] However, more recent studies in human volunteers showed that endotoxin tolerance can be induced but that challenges of *S typhi* still produced the febrile and toxic manifestations of enteric fever.[28] Moreover, one study investigating typhoid fever and disseminated intravascular coagulation suggested that neither endotoxemia nor bacteremia played a major pathogenic role in this disease.[43] Although the exact pathogenesis of enteric fever remains unclear, it is possible that endotoxin may still play a role, possibly at the local tissue level.[42]

Clinical Spectrum and Management of Salmonellosis

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Salmonella INFECTION may appear to be one of several distinct clinical syndromes, or symptoms may overlap in its clinical presentation. The major disease states produced by salmonellosis are enterocolitis (gastroenteritis), enteric fever, bacteremia, focal infection and chronic carrier state.

Enterocolitis

Localized acute intestinal infection is the most common form of salmonellosis.[29,38] In the small

intestine, epithelial invasion occurs but without extensive destruction of intestinal mucosa.[44] The organisms reach the lamina propria where they multiply and elicit an inflammatory response. In *S typhi,* this response may trigger production of predominantly mononuclear cells, whereas nontyphi *Salmonella* infection generally evokes polymorphonuclear neutrophilic reaction. It is also now known that colonic involvement occurs with acute salmonellosis (hence the term "enterocolitis"); histological changes include edema, inflammation, erosion and microabscesses.[45]

Nontyphi *Salmonella* serotypes, particularly *S typhimurium,* are most commonly responsible for acute enterocolitis.[29,38] Although *S typhi* may produce enterocolitis and cause diarrhea, constipation may be an equally or a more common gastrointestinal symptom with this strain of *Salmonella.*[46,47] Clinical expression of acute enterocolitis may occur as soon as 8 hours or as late as 72 hours following ingestion of *Salmonella* organisms.[48] Symptoms may begin with transient nausea and vomiting followed by myalgia, headache, fevers, chills, diarrhea and abdominal cramps.[18] Generally, the stools are not bloody, are of moderate volume and loose in character. Occasionally, the discase may be severe, associated with fluid and electrolyte depletion leading to hypovolemic shock, blood loss, toxic dilatation of the colon[45] or bacteremia, particularly in those patients with increased susceptibility to salmonellosis. Symptoms of fever last less than 48 hours and diarrhca usually abates within one week, although patients with colonic involvement, intra-abdominal suppuration or other complications may have a prolonged course of fever, loose stools and abdominal complaints.

Diagnosis is made by isolating the pathogen by stool culture. Except for *S typhi* cases, blood cultures generally are nonrewarding. Serological tests for antibodies to O and H antigens are of limited value. Follow-up of these patients will show that stool cultures may remain positive in up to 65 percent of cases during the second or third week after onset of illness, even though most patients are asymptomatic.[36,37] In untreated patients, fecal excretion of nontyphi salmonellae beyond two months may occur in up to 25 percent of cases. By six months all stool cultures are generally negative for these organisms. Chronic carrier states of nontyphi salmonellae are uncommon but do occur.[18,49]

Management will depend on severity of illness and any associated complications. For severe cases of diarrhea, fluid and electrolyte replacement is the single most important modality of therapy. Antiperistaltic agents to decrease diarrhea are generally not recommended. Most cases of enterocolitis will not require antimicrobial therapy. In fact, chemotherapy prolongs excretion of nontyphi *Salmonella* organisms and symptoms remain unchanged when compared with untreated controls.[36,37] However, in severely ill patients in whom bacteremia, enteric fever or metastatic focal infections develop, or who have impaired host resistance (such as malignancy, immunosuppression, sickle cell disease), antimicrobial therapy should be initiated (specific drug therapy will be discussed in the section on enteric fever). Moreover, if gastroenteritis is caused by *S typhi,* it may be advisable to treat patients with even mild diseasc because (1) enteric fever is more likely to occur with *S typhi* than with other serotypes, (2) patients with prolonged fecal excretion of the organism related to antimicrobial therapy are almost always those infected with nontyphi *Salmonella* and not *S typhi* and (3) most chronic carriers of salmonellosis are found to be infected with *S typhi* serotype. However, the recommendation to treat mild *S typhi* gastroenteritis is not accepted by most clinicians.

Enteric Fever

Enteric fever is clinically caused by *S typhi* and hence called typhoid fever. A clinical syndrome nearly identical to typhoid fever but caused by *S paratyphi* A, B or C was previously designated paratyphoid fever. However, because other serotypes may also cause enteric fever, it is more conventional now to ascribe paratyphoid fever to any serotype other than *S typhi* causing this syndrome.

Following ingestion of the organism, an incubation period of approximately ten days may be followed by bacteremia and the onset of the clinical features of enteric fever. The major clinical features of enteric fever are shown in Table 2. Four series of enteric fever reported in the literature were selected to illustrate similarities and differences in incidence of clinical findings. Series 1 represents an epidemic before the era of modern antimicrobial therapy[46]; series 2 represents an epidemic occurring in the United States in the modern chemotherapy period[50]; series 3 is made up of cases of enteric fever where the disease is endemic,[51] and series 4 illustrates features found in sporadic cases of enteric fever.[52] As noted in

TABLE 2.—*Clinical Features of Enteric Fever*

Clinical Features	Percent of Patients			
	Series 1*	Series 2†	Series 3‡	Series 4§
Symptoms				
Fever	100	93	98	100
Chills	37	37	NR	78
Headache	90	59	75	78
Diarrhea	43	57	37	44
Constipation	79	10	17	48
Nausea	54	23	NR	44
Vomiting	54	35	24	NR
Abdominal pain	19	39	52	37
Cough	86	28	53	56
Signs				
Rose spots	33	13	0	11
Hepatomegaly	25	52	NR	19
Splenomegaly	64	42	NR	30
Neurologic findings	12	5	33	NR

NR = not reported

*Stuart and Pullen: 1934-1944, epidemic of 360 cases.[46]
†Hoffman et al: 1973, epidemic of 105 cases.[50]
‡Wicks et al: 1966-1969, endemic outbreak of 265 cases.[51]
§Briedis and Robson: 1961-1977, 27 sporadic cases.[52]

Table 2, fever, chills, headache and gastrointestinal symptoms are the most important presenting complaints of patients with enteric fever. Interestingly, cough and bronchitic symptoms occur in more than half of the patients, but documented pneumonia is uncommon.[46,50] A variety of other nonspecific complaints such as myalgia, arthralgia, weakness or sore throat may also occur. Physical findings are primarily limited to the abdomen. Abdominal distention, tenderness and hypoperistalsis; hepatomegaly, and splenomegaly vary in frequency, but may be present. Classic rose spots (2- to 4-mm erythematous maculopapular lesions that blanch on pressure) may appear transiently on the upper abdomen but are infrequently observed in most reported series.[53] Relative bradycardia, another feature classic of typhoid fever, has been observed in only a third of cases.[51] Although paratyphoid fever is nearly identical to typhoid fever in its clinical features,[54,55] relative bradycardia has been reported in 50 percent to 100 percent of cases. Neuropsychiatric manifestations of enteric fever are nonspecific but may occur in up to 75 percent of patients.[56] Confusion, stupor and delirium are the most common findings, occurring in more than 50 percent of cases.[46,56] Other diffuse and focal neurological deficits and gross schizophrenic psychoses have also been reported.

Complications of enteric fever, other than death, can be classified as abdominal or extra-abdominal. In the era before antibiotics, mortality from enteric fever was 10 percent to 15 percent.[46] With antimicrobial therapy and supportive care, mortality should be nearly zero.[50] Abdominal complications that are most serious are intestinal perforation (1 percent to 5 percent) and intestinal hemorrhage (1 percent to 21 percent).[57] Complications occurring outside the abdomen include the previously mentioned neuropsychiatric features, localized infections (meningitis, endocarditis, arthritis, osteomyelitis, pneumonia), bone marrow suppression, parotitis, decubitus ulcer, renal failure and chronic carrier state.[51,58]

Diagnosis of enteric fever is primarily made by blood cultures. During the first week of illness, blood cultures are positive in 55 percent to over 80 percent of patients.[46,50] By the third week of illness, blood culture positivity diminishes to 30 percent to 40 percent. During this period, stool cultures are most rewarding, with a yield of nearly 75 percent (Figure 1). Late in the disease, bone marrow cultures may yield the pathogen.[59] Serological studies measuring fourfold or greater rises in agglutinins against the O and H antigens are unreliable[50] and are not recommended as a basis for diagnosis.[60] Management of enteric fever should be directed towards antimicrobial therapy, supportive care and the treatment of complications and extra-abdominal infections.

The antimicrobial chemotherapy that has been used to treat enteric fever has been primarily chloramphenicol, ampicillin or trimethoprim-sulfamethoxazole. Although other antimicrobial agents such as aminoglycosides may be active in vitro against *Salmonella* organisms,[61] clinical experience is too limited to recommend these agents for treatment of salmonellosis. Cephalosporins, such as cefazolin, have been used in a small number of patients with promising results.[62] At present, chloramphenicol remains the drug of choice for enteric fever.[63] The recommended dosage is 50 mg per kg of body weight per day in four divided doses for at least 14 days, taken orally. However, if patients are ill enough to be admitted to hospital, chloramphenicol should be administered intravenously. One study states that orally given chloramphenicol provides higher blood levels than parenteral chloramphenicol and therefore is more effective in treating typhoid fever.[64] These investigators, however, administered chloramphenicol succinate intramuscularly. It is now known that the succinate form of this drug produces only half the blood level of drug compared with orally given chloramphenicol because of the failure of the suc-

cinate to hydrolyze.[65] Chloramphenicol succinate, therefore, is not recommended by the manufacturer for intramuscular administration.[66] Moreover, the fatal aplastic anemia associated with chloramphenicol appears to be seen almost exclusively with oral administration of the drug.[67,68] At this institution, it is our recommendation to administer chloramphenicol only by the intravenous route. The response rate of salmonellosis to this drug has been excellent (unpublished data).

Ampicillin in a dose of 100 mg per kg of body weight per day (up to 200 mg per kg per day given parenterally in severely ill patients) in four divided doses either orally or intravenously for two weeks is also effective for treating enteric fever. The clinical response appears to be somewhat slower than with chloramphenicol[50,59,69]; however, the relapse rate may be lower with ampicillin (5 percent) than with chloramphenicol (10 percent). Amoxicillin, an ampicillin analogue, also appears to be effective in treating enteric fever.[70,71,72] Trimethoprim-sulfamethoxazole has been shown to be effective in treating typhoid fever, provided that the dosage is sufficient.[70,73,74] The recommended dose is 320 to 640 mg of trimethoprim with 1,600 to 3,200 mg of sulfamethoxazole in two to four divided doses (four to eight tablets of 80 mg of trimethoprim and 400 mg of sulfamethoxazole) for two weeks.

Salmonella typhi resistance to antimicrobial agents, especially chloramphenicol, has been reported from Mexico,[75] Vietnam,[76] Korea[77] and parts of the United States.[78,79] The mechanism of drug resistance appears to be primarily R-factor mediated, which is transferable[80] and often associated with multiple drug-resistance patterns.[75,77,78] Resistance to ampicillin may also occur, but less often than to chloramphenicol. Trimethoprim-sulfamethoxazole resistance of *S typhi* and other *Salmonella* species is uncommon even though resistance to sulfonamides alone may be present.[81] In patients with enteric fever from areas where chloramphenicol resistance is endemic, initial therapy before data are available about organism susceptibility should be carried out with ampicillin or amoxicillin. If a strain of *S typhi* resistant to both chloramphenicol and ampicillin is isolated, trimethoprim-sulfamethoxazole should be administered.

Supportive care for enteric fever includes proper hydration, maintenance of adequate perfusion and observation for complications. In very sick patients, a short course of corticosteroids may be lifesaving. Prednisone in a dose of 40 mg to 60 mg per day for *not more than three days* is recommended.[57] Intestinal perforation is a complication that is associated with high mortality. Controversy exists over whether medical or surgical therapy is the best approach to managing this problem. Those who advocate medical therapy recommend antibiotics, general supportive care and nasogastric suction.[57] Surgical treatment is reserved for deterioration of a patient's condition while on medical therapy or for development of abscess or adhesions. Proponents of immediate surgical intervention for all cases of typhoid intestinal perforation justify these recommendations by operative findings of open perforation or gangrene in 96 percent of cases.[82] Moreover, intestinal flora other than *Salmonella* will have contaminated the peritoneum following perforation and may lead to peritonitis and sepsis. Under these conditions, such additional antimicrobial therapy as aminoglycosides and clindamycin (if chloramphenicol is not already being administered) may be essential.

Intestinal hemorrhage generally is not massive and will respond to medical therapy. Occasionally, surgical intervention may be required. Such extra-abdominal complications as meningitis, endocarditis, osteomyelitis or arthritis should be managed in the standard manner appropriate for these infections.

Bacteremia and Focal Infection

Bacteremia from nontyphi *Salmonella* organisms occurs most commonly in patients with sickle cell disease, hemolytic anemia, malignancy, and liver and gallbladder disease.[32,33,83] The frequency of bacteremia or sepsis is 5 percent to 10 percent.[29,38] The clinical manifestations of bacteremia are identical to the classic Gram-negative bacillemia seen with other enteric organisms. Bacteremia can follow enterocolitis and lead to focal infections or be associated with extraintestinal sites of infection. Focal infections associated with nontyphi *Salmonella* include endocarditis, pericarditis, appendicitis, cholecystitis, salpingitis, intra-abdominal abscess, pneumonia, urinary tract infection, bone and joint infection, meningitis and mycotic aneurysm.[29,31,84,85] Such unusual infections as empyema, myocardial abscess and Reiter syndrome have been reported with salmonellosis.[86-88] Diagnosis of *Salmonella* bacteremia or

local infection, or both, can be made by isolation of the pathogen from blood or infected focal site(s).

Antimicrobial therapy for bacteremia and focal infections is the same as for enteric fever. However, with endocarditis and mycotic aneurysm secondary to salmonellae, a bactericidal agent such as ampicillin is preferred to chloramphenicol. Focal infections such as abscesses should be drained. Duration of therapy will depend on the site of the infection involved and on clinical response. Bacteremia alone without focal infection should be treated with antimicrobial drugs for 10 to 12 days.

Chronic Carrier State

The chronic carrier state is defined as the excretion of *Salmonella* for more than one year. Chronic enteric carriers who excrete organisms in the feces are the most common, although occasionally chronic urinary carriers are found. Chronic carriers are asymptomatic.

The chronic carrier state occurs more frequently following *S typhi* infection; the incidence is 2 percent to 4 percent.[89,90] Chronic carriers following nontyphi salmonellosis is uncommon.[49] The chronic enteric carrier state of *Salmonella* increases with age and is associated with biliary tract disease. A chronic urinary carrier state is more commonly associated with schistosomiasis of the urinary tract.

Diagnosis of a chronic carrier state is made by repetitive isolation of the organism for over one year. Management should be directed first toward determining the presence or absence of biliary tract disease. The antimicrobial drug of choice is ampicillin (not chloramphenicol, which has a poor success rate). In the presence of gallbladder disease, ampicillin in dosages of 6 to 8 grams per day plus 2 grams of probenecid (both drugs given in four divided doses) is started two to three days before operation. The diseased gallbladder is surgically removed and ampicillin is continued for two weeks postoperatively.[90] If biliary tract disease cannot be detected by roentgenogram (biliary tract carrier with normal cholecystogram or possibly hepatic carrier) or if fecal excretion of organisms continues postcholecystectomy (hepatic carrier), long-term administration of ampicillin is recommended.[91] Two effective regimens are 6 grams of ampicillin per day given orally plus 2 grams of probenecid in four divided doses for six weeks[91] or 3 grams per day given intravenously in three divided doses for two weeks.[92] Trimethoprim-sulfamethoxazole, 320 mg of trimethoprim and 1,600 mg of sulfamethoxazole in two divided doses for three months, also appears promising.[93]

Precautions and Recommendations for Travel

Because food and water are the major vehicles for transmitting salmonellae, proper sanitation and hygiene are extremely important in prevention of this disease. In countries where salmonellosis is endemic, all food should be properly cooked (particularly fowl, egg products and foods containing unpasteurized milk), and water should be boiled.[17] If travel to foreign countries is contemplated, the nearest United States Public Health Service office should be contacted to determine if typhoid vaccine (and other immunoprophylaxis) is recommended. The vaccine is given as two injections (0.5 ml) a month apart, or three injections at weekly intervals if time does not allow a four-week schedule. The vaccine is effective for three years and a single booster is recommended after this period.[94]

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Refer to: Park R: Lactic acidosis—Medical Staff Conference, University of California, San Francisco. West J Med 133:418-424, Nov 1980

Lactic Acidosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *In this conference we will discuss an important form of metabolic acidosis, lactic acidosis. Dr. Robert Park, Assistant Professor of Medicine and a member of the Renal Division at the San Francisco Veterans Administration Medical Center, will make the presentation.*

DR. PARK:† Lactic acidosis was introduced as a clinical entity by Dr. William Huckabee approximately 20 years ago. Since then, this interesting metabolic disorder has become one of the most common forms of metabolic acidosis encountered in clinical medicine. This heterogeneous disorder has a clinical spectrum diverse in both etiology and pathogenesis.[1] During this session, I should like to review briefly some clinical features of the syndrome and spend the remaining time discussing recent advances that have helped physicians to understand further the abnormalities of lactate metabolism in this disease. We hope these advances will provide a basis for successful therapy for this usually fatal disorder.

Classification

The knowledge we have gained about this disease in the last 20 years has enabled us to update Huckabee's original classification. I should like to start with the classification so that we have a common ground of nomenclature (Table 1). This classification was proposed by Cohen and Woods in 1976[2] and is a clinically functional one. It has gained wide acceptance, both in this country and in Europe, and describes two basic types of lactic acidosis.

Type A includes those cases in which hypoperfusion or hypoxemia is clinically evident. This is the type that may develop during conditions of shock such as severe cardiac failure. It is the most common type of lactic acidosis encountered clinically today and has a mortality greater than 80 percent. Type B lactic acidosis includes all other cases and is subdivided into three different categories. Type B 1 occurs in association with various systemic diseases such as diabetes, liver disease, renal insufficiency and infection. These diseases are thought to predispose to the development of lactic acidosis although the reason for this is not known. Type B 2 is associated with drugs and toxins such as phenformin, ethanol and fructose. Before 1977 phenformin, taken orally, was used throughout the world as a hypoglycemic agent. Because of the unacceptably high association of phenformin with the occurrence of lactic acidosis, this drug was withdrawn from the market by the Food and Drug Administration. As a result, the frequency of phenformin-associated lactic

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†Robert Park, MD, Assistant Professor of Medicine.

ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
DCA = dichloroacetate
NAD = nicotinamide-adenine dinucleotide
NADH = reduced NAD
pHi = intracellular pH
TRIS = tris(hydroxymethyl) aminomethane

acidosis has notably declined. Yet phenformin is still used in Europe and other parts of the world. Type B 3 lactic acidosis includes those varieties that occur in association with congenital errors of metabolism.

Clinical Features

Let us now briefly review some clinical features of this interesting syndrome (Table 2). Typically, the onset may be rather abrupt, often occurring within a matter of several hours. It is often stated that the onset is accompanied by an altered state of consciousness ranging from mild lethargy to frank coma. Hypotension and evidence of hypoperfusion are seen initially only in type A lactic acidosis. The hallmarks of this disease are the signs and symptoms that relate to metabolic acidosis. These include Kussmaul-type hyperventilation and hyperkalemia, both of which occur in response to the severe acidosis.

The metabolic acidosis provides the first clue to the diagnosis because it is an acidosis of the anion gap variety. Table 3 lists most of the common clinical causes of the anion gap type of acidosis. The anion gap is simply the difference between the sum of major cations in the blood (sodium and potassium) less the sum of major anions in the blood (chloride and bicarbonate). In most normal situations the difference approximates 15 ± 3 mEq per liter. In acidosis with an anion gap of 20 mEq per liter or greater, one must identify the anion. The most common form of anion gap acidosis today is probably diabetic ketoacidosis in which the ketones β-hydroxybutyrate and acetoacetate represent the missing anions. Uremic acidosis is also a very common cause of anion gap acidosis; the missing anions here are mainly phosphates and sulfates that accumulate in the extracellular fluid. Drugs and toxins frequently cause anion gap acidosis. Salicylates represent the anion in cases of salicylic acid poisoning. Methanol ingestion, in which the anion is probably formate, and ethylene glycol ingestion, in which the missing anion is oxalate, are additional causes. Finally, of course, in lactic acidosis, lactate makes up the bulk of the missing anion.

TABLE 1.—*Classification of Lactic Acidosis**

Type A
Poor tissue perfusion

Type B
1. Various common disorders, such as diabetes, liver disease, renal insufficiency, infection
2. Drugs and toxins, such as phenformin, ethanol, fructose
3. Hereditary forms

*Source: Cohen RD, Woods HF.[2]

TABLE 2.—*Clinical Features of Lactic Acidosis*

Onset may be abrupt
Altered state of consciousness
Hypotension initially in type A lactic acidosis
Metabolic acidosis
  Kussmaul hyperventilation
  Hyperkalemia
>80 percent mortality

TABLE 3.—*Causes of Anion Gap Acidosis*

Diabetic ketoacidosis	β-hydroxybutyrate, acetoacetate
Uremic acidosis	Phosphates, sulfates
Drugs and toxins	Salicylates, methanol, ethylene glycol
Lactic acidosis	Lactate

$$\text{Anion Gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-) = 15 \pm 3 \text{ mEq per liter}$$

Diabetic ketoacidosis, uremic acidosis and acidosis associated with ingestion of drugs or toxins can usually be easily excluded by history, physical examination and routine laboratory tests. The diagnosis of lactic acidosis can be confirmed by finding an elevated concentration of 4 to 5 mM of lactate in arterial blood. In most cases of lactic acidosis, the lactate level is 10 to 30 mM, and there is a reciprocal decrease in the bicarbonate concentration and in the arterial pH to values less than 7.3.

This disease has long intrigued clinicians and students of biochemistry because the biochemistry of lactate metabolism holds the key to understanding the disorder. For this reason, I would like to discuss a few basic features of lactate metabolism as they relate to the pathophysiology of lactic acidosis.

Lactate Metabolism

Figure 1 illustrates the Cori cycle in schematic form. The Cori cycle is the normal interorgan balance of lactate. Lactate is an end product of

anaerobic glucose metabolism. Although it is produced by most tissues in the body, the skin, muscle, erythrocytes, brain and intestinal mucosa are most active in its production. Under basal conditions these tissues produce approximately 1,300 mmoles of lactate per day. The liver and the kidney are the two tissues that metabolize the lactate, with the liver being predominant in this function. The liver takes up approximately 60 percent of the 1,300 mmoles of lactate produced per day, and converts most of it back to glucose, which is then recycled. There are two points in Figure 1 that deserve emphasis. First of all, the figure shows estimates of how much these tissues contribute to lactate production and utilization under basal conditions. In certain circumstances, tissues may increase their production of lactate severalfold, perhaps even an order of magnitude. Likewise, the liver has an enormous capacity to use lactate. Measurements in humans and animals have shown that the capacity of the liver to metabolize lactate approximates 3,000 to 4,000 mmoles per day under normal circumstances. As we will see later, this large capacity plays a very important role in the pathogenesis of lactic acidosis. Figure 1 also shows the prominent role the liver plays in daily acid-base balance in the body, producing and using 60 percent of the body's lactate each day. If one calculates 60 percent of 1,300 mmoles of lactate used each day, the liver extracts approximately 70 mEq of lactate every two hours. In other words, in two hours the liver metabolizes sufficient hydrogen ion in the form of lactate to equal the total daily net acid excretion by the kidney. This fact should serve to illustrate that the role of the liver in daily lactate balance assumes an additional and very prominent role in overall acid-base balance.

The normal concentration of lactate in extracellular fluid is about 1 mM. As can be appreciated by the cyclic nature of the Cori cycle (Figure 1), the 1-mM concentration represents a balance between the rate of production by skin, muscle and erythrocytes, and the rate of utilization by the liver and kidney. The pathogenesis of lactic acidosis might therefore be simply visualized as an imbalance between the two relative rates of production versus utilization.

Because lactate is an end product of metabolism, it can only be derived from pyruvate in a reaction catalyzed by the enzyme lactate dehydrogenase (Figure 2). This is a cytosolic enzyme present in virtually all tissues. The reaction requires the cofactor NAD (nicotinamide-adenine dinucleotide) as a hydrogen acceptor. The equilibrium of this reaction strongly favors lactate, so that in arterial blood the concentration of lactate (1 mM) is about tenfold greater than that of pyruvate (0.1 mM). Because this reaction is virtually in equilibrium at all times, it may be expressed in terms of a mass action equation (Figure 2), so that the concentration of lactate at

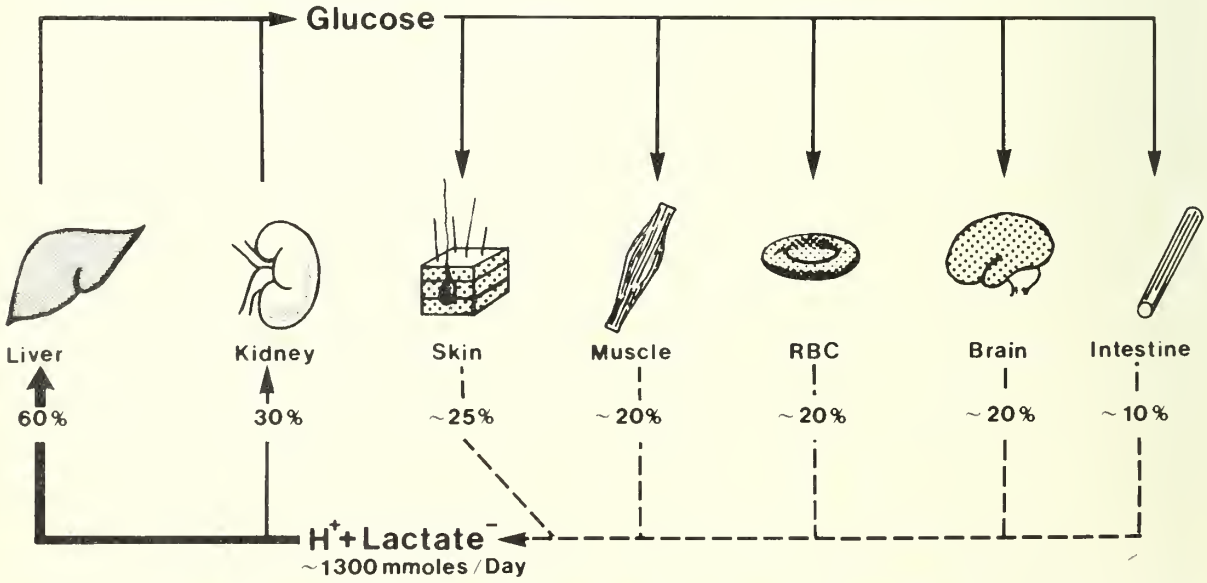

Figure 1.—A schematic representation of the Cori cycle. Tissues such as skin, skeletal muscle, erythrocytes (RBC), brain and intestinal mucosa convert glucose into lactate by anaerobic glycolysis. Liver and kidney together utilize 90 percent of the lactate produced and recycle most of it back to glucose by glyconeogenesis.

any given time is a function of three variables: the pyruvate concentration, the ratio of reduced NAD (NADH) to NAD (redox state) and the intracellular hydrogen ion concentration.

Because lactate is an end product, its disposal depends on the disposal of pyruvate. In Figure 3, we see that, unlike lactate, pyruvate is not an end product of metabolism, but rather it is a key intermediate at the junction of several important pathways. These include (1) glycolysis, in which pyruvate is formed from the oxidation of glucose, (2) glyconeogenesis, whereby pyruvate is the initial substrate in the pathway to reform glucose, (3) transamination, in which pyruvate interconverts with amino acids such as alanine and (4) oxidation, in which pyruvate is ultimately oxidized via the Krebs cycle to yield carbon dioxide, water and energy in the form of adenosine triphosphate (ATP). What are the activity and direction of these various pathways in tissues as they relate to the metabolism of lactate? Tissues such as skin, skeletal muscle, brain, and intestinal mucosa, as well as erythrocytes, are generally characterized by high rates of glycolysis. In these structures, the flow of glucose is preferentially directed toward lactate formation via pyruvate. Quantitatively, about 60 percent or more of the lactate taken up by the liver is reconverted to glucose by glyconeogenesis.

$$\text{(1)}\quad \underset{\sim 1\text{mM}}{\text{Lactate} + \text{NAD}} \underset{}{\overset{\text{LD}}{\rightleftharpoons}} \underset{\sim 0.1\text{mM}}{\text{Pyruvate} + \text{NADH} + \text{H}^+}$$

$$\text{(2)}\quad [\text{Lactate}] = [\text{Pyruvate}] \times \text{Keq}\ \frac{[\text{NADH}]\ [\text{H}^+]}{[\text{NAD}]}$$

Figure 2.—Mass action equation for lactate-pyruvate equilibrium. H^+ = proton; LD = lactate dehydrogenase; NAD = nicotinamide-adenine dinucleotide, and NADH = reduced NAD.

Pathophysiology

Given this framework of lactate metabolism, we can use the Cori cycle (see Figure 1), to help us visualize the pathophysiology of lactic acidosis quite simply as a pathologic derangement of the normal metabolic pathways of lactate; that is, lactic acidosis represents an imbalance between the rate of production by tissues active in glycolysis (such as skin and skeletal muscle) and the rate of utilization by tissues active in glyconeogenesis (liver and kidney) so that lactate accumulates. This may occur in the following manner. If there is enhanced glycolysis by skin, muscle, erythrocytes and brain at a time when lactate utilization by the liver remains constant,

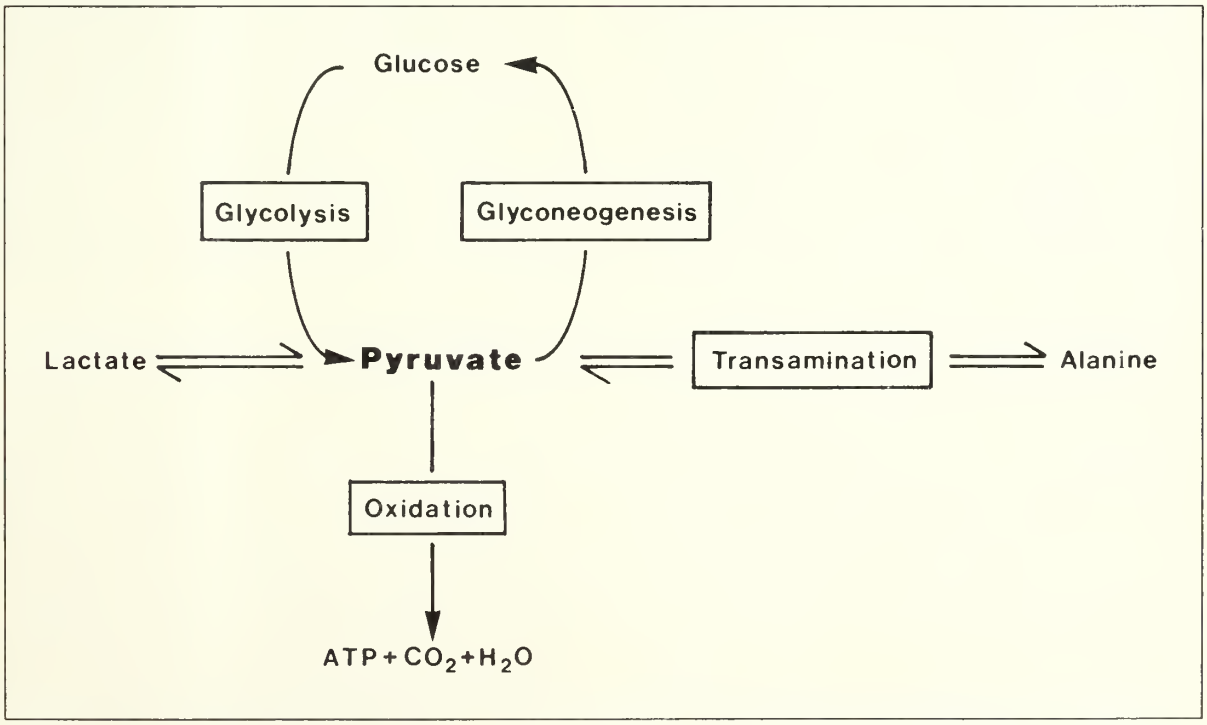

Figure 3.—A simplified diagram to illustrate the relationship of lactate and pyruvate to major metabolic pathways including glycolysis, glyconeogenesis, transamination and oxidation.

remains relatively unchanged. This emphasizes that the therapy to date is basically inadequate. The mortality exceeds 50 percent in phenformin-associated lactic acidosis,[9] and in type B 1 lactic acidosis the mortality exceeds 85 percent. The mainstay of therapy for lactic acidosis has been the administration of large amounts of sodium bicarbonate. This is a symptomatic therapy; it merely treats the acidosis. What are some of the other aims of treatment? The first is to eliminate the known drugs and toxins that are thought to be associated with lactic acidosis (such as phenformin, ethanol and fructose); the second is to restore tissue perfusion and oxygenation, especially in type A lactic acidosis, and the third is to correct the acidosis to a pH of greater than 7.1. This is important because there is a significant compromise in cardiac contractability with more severe degrees of acidosis. Furthermore, the data of Lloyd and co-workers suggest that below this extracellular pH of 7.1 the liver pHi may be decreased, thus inhibiting lactate utilization.[8]

Some other forms of therapy have been used in this syndrome. Therapeutic approaches using dialysis, the buffer TRIS (tris[hydroxymethyl] aminomethane), methylene blue or nitroprusside really have not been adequately tested, so we cannot say much about their efficacy in this disease. Insulin and glucose therapy have probably been effective mainly in phenformin-induced lactic acidosis. The drug dichloroacetate (DCA) is still an investigational drug, but promises the greatest potential benefit to this disorder. This interesting drug has a variety of metabolic effects—it lowers blood glucose, decreases blood lactate and pyruvate, decreases plasma cholesterol and triglycerides, and in some preliminary studies it has been shown to reduce blood lactate levels in experimental phenformin-induced lactic acidosis.[10-12] The effect of DCA on blood lactate is probably mediated by activation of pyruvate dehydrogenase, the enzyme that regulates the entry of pyruvate into the Krebs cycle. Because of this activation, there is enhanced oxidation of lactate and pyruvate in peripheral tissues such as skeletal muscle. Consequently, the release of these substrates is attenuated, and blood lactate levels decrease.

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Important Advances in Clinical Medicine

Epitomes of Progress — Orthopedics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in orthopedics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

The Metabolic Energy Crisis Following Lower Extremity Injury

LEVEL WALKING is perceived as requiring minimal exertion. At a normal walking speed (75 to 90 m per minute), the average adult uses oxygen at the rate of 13 ml per kg of body weight per minute. This represents less than 40 percent of the maximal aerobic capacity for most untrained persons under 60 years of age. Below the anaerobic threshold (approximately 50 percent) most energy is supplied by aerobic metabolic pathways; thus, persons can exercise many hours without exhaustion. Above this limit, anaerobic processes increasingly are brought into play and endurance is progressively limited by acidosis and the limited energy supply associated with anaerobic metabolism.

In a study of normal persons subjected to 21 days of bed rest, the aerobic capacity dropped 26 percent and was only restored to normal after a 50-day physical conditioning program. Thus, the effects of blood loss and negative nitrogen balance in patients confined to bed with multiple injuries may easily reduce aerobic energy production capability by half.

Walking with crutches increases energy requirements. Even among trained users of crutches, the four-point gait without bearing weight on one limb increases metabolic demands to 75 percent of aerobic capacity.

Casts, joint pain and loss of joint motion all contribute to increased energy cost. Most patients walking without assistance choose a slow walking speed to keep expenditure of energy to within normal limits. For example, hip pain or loss of knee motion can double the energy required for walking.

Energy cost studies have led to the following clinical conclusions:

- The patient should be mobilized at the earliest possible time to prevent the debilitating effects of prolonged bed rest.
- Progressive weight-bearing on the limb should be allowed as soon as possible to decrease the exertion required by use of crutches.
- Joints should be mobilized as early as possible to reduce energy cost. Particular effort should be made to mobilize the knee by the use of a cast brace or patellar tendon-bearing cast.
- A program of physical conditioning may be

helpful to restore the patient to his or her level of fitness before injury.

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Nuclear Medicine and Bone Cancer

BONE SCANS are useful in evaluating primary bone tumors as well as bone pain that may be caused by metastatic lesions.

Studies are done with bone scanning agents, such as diphosphonate labeled with technetium 99m (which depends on osteoblastic activity, new osteoid formation and blood flow) and gallium citrate Ga 67 (which accumulates in inflammatory and neoplastic lesions).

Solitary, rather than multiple, metastatic lesions of the bone are more often a diagnostic problem. About 30 percent of metastatic lesions observed on bone scans are solitary. About 50 percent to 65 percent of all solitary lesions are metastatic, most likely originating from the breast, lung or prostate, but also from the cervix, colon, kidney, skin, rectum, skeletal muscle and reticuloendothelial system. About half are in the spine, the rest divided between the extremities and skull. About 10 percent to 40 percent of these lesions will be missed by radiographic studies. Because of the nonspecificity of increased diphosphonate ^{99m}Tc uptake, these cases should have histological proof to confirm the diagnosis.

Benign bone tumors, such as osteochondromas, endochondromas, fibrous dysplasia, eosinophilic granulomas, Paget disease of bone and osteoid osteomas, are usually detected on diphosphonate ^{99m}Tc scanning, some as intense in uptake of the agent as malignant tumors. Simple or aneurysmal cysts and cortical defects found on scans in children show decreased or normal activity, unless there is an associated fracture.

Primary osteosarcomas are usually positive on scanning, showing intensely increased uptake of the agent, and in some showing activity extending along uninvolved bone. Citrate ^{67}Ga imaging is also positive and better delineates the lesion. These lesions metastasize to the lung before bone, and they are best identified radiographically. However, some lung lesions have been detected by citrate ^{67}Ga imaging, while no abnormalities were found on radiographic studies.

Almost 100 percent of Ewing sarcomas are identified equally well by radiographic studies, bone scanning or citrate ^{67}Ga imaging. They metastasize to bone before soft tissue. Diphosphonate ^{99m}Tc, which is more sensitive than citrate ^{67}Ga or radiography, is helpful in identifying the 30 percent of cases with asymptomatic distant lesions.

Only about 50 percent of multiple myeloma lesions give positive scans, which may still be valuable in patients with back pain and negative radiographic findings.

Three to four months after radiation therapy, there may be decreased, then increased activity—after that, however, bone scans are useful in evaluating the therapeutic response.

Bone scans which reflect physiological changes often show abnormal findings before radiographic studies, which require significant calcium loss. Thus, scans are indicated in cases of bone pain with negative radiographic findings, and for skeletal screening for asymptomatic lesions.

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Examination of an Unstable Knee

MOTION BETWEEN two bodies can occur along six planes. The planes of knee motion are flexion/extension, abduction/adduction (valgus/varus), external/internal rotation, anterior/posterior translocation, medial/lateral translocation and compression/distraction. Motion is described as tibia motion in relation to the femur. Motions quantified in a clinical examination are flexion/extension, abduction/adduction and anterior/posterior translocation. Abnormal rotatory motion is also noted. The knee is stabilized by the joint surface contours, menisci, ligament restraints and muscle action. Stability from joint surface contours is minimized when the joint is unloaded.

Several maneuvers have been developed to provoke anterior displacement of the tibia in early flexion (pivot shift, jerk test, Losee test, flexion rotation drawer test). A slight valgus stress is

applied, and with initial knee flexion the tibia internally rotates and subluxes anteriorly. At 20 to 30 degrees of flexion, the tibia shifts back to its normal position. The abnormal forward tibial subluxation is not possible in the presence of a competent anterior cruciate ligament.

Instability may be present in one or more planes. Common one-plane instabilities are valgus, varus, anterior and posterior. In rotatory instability, the axis of knee motion changes from its normal intercondylar position. The instability may be described by noting which plateau of the tibia rotates into an abnormal position. For example, if the tibia externally rotates with the lateral tibial plateau moving posteriorly, the knee is rotating around an axis through the medial compartment, and the instability is described as posterior lateral rotatory instability (posterior refers to the direction of the displacement and lateral refers to which tibial plateau is moving). Common rotatory instabilities are anteromedial, anterolateral and posterolateral. A combined instability is described by listing the planes of instability.

DALE M. DANIEL, MD

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Physiology of Warm-ups and Exercise

No matter how well conditioned an athlete is, he or she must warm up before strenuous exercise to avoid injury. The amount of warm-up needed, however, is directly influenced by the degree of conditioning maintained.

Conditioning requires a minimum of six weeks of physiological preparation of the muscles, joints and connective tissue to withstand the stresses of concentrated demands. The entire body should be involved to improve balance, rhythm and alignment. In tests done at the National Athletic Health Institute's Biomechanics Laboratory, it has been found that professional athletes benefit most from continuing the same sports, or movements therefrom, throughout the year, in season and out.

It appears that athletes who drop out of training during the off-season have a little more trouble each year returning to optimum playing condition. Some never quite reach their previous level of excellence. In contrast, those who maintain proper conditioning all year round will find it easy to reach playing form. Equally important, they enjoy their careers through the years that once would have found them in broadcasting booths. Perhaps this explains the increasing population of relatively older athletes who continue to lead in the leagues.

As for warming up, amateurs are tempted to underrate its importance from time to time, so the following explanation may be useful.

Warm-up exercises benefit athletes by calling into use the atavistic mechanisms of increased metabolism, more rapid exchange of oxygen from the blood of the tissues, and an increase in the efficiency and speed of nerve conduction to the warmed tissues. Tissue fiber articulation is improved and the viscosity of joint fluids is decreased, allowing for more rapid motion.

But, why work so hard at it? If it is the higher temperature that tends to increase the rate of metabolic chemical reactions in the working muscles, why not just have a warm bath? Some 30 years ago Swedish researchers studied this idea by comparing the effect of heating an athlete's body passively in a sauna before a race, with that of raising the body's temperature with slow running and calisthenics. Although they did not understand why, they found the sauna exposure much less effective. These same investigators also observed better results after a 15-minute warm-up than after a 5-minute one, but no increase in benefits when warm-up times went to 30 minutes.

Since that time, it has been determined that muscular exercise performed during warm-up causes a shift in the pattern of distribution of blood flow in the body. One aspect of this is increased flow to the vascular beds of the working muscles and decreased flow to the skin and viscera. It is thought that this permits a greater cardiac output than would occur without warm-up.

Another recent observation supports the hypothesis that prostaglandins formed in the vascular bed itself may contribute to the adaptation of blood flow in the person who is working out.

In any case, according to Barnard and colleagues, strenuous exercise without warm-up induced abnormal electrocardiographic (EKG) changes in 70 percent of 44 normally asymptomatic subjects, aged 21 to 52 years. However, as little as two minutes of jogging in place as a

warm-up eliminated or reduced these abnormal EKG responses.

Therefore, of the few important rules to be observed by any fitness buff, proper warming up probably pays the highest dividends per moment spent.

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Sarcoma of Bone: Current Management

IN THE LAST DECADE a dramatic change has taken place in the prognosis for some bone sarcomas. This has resulted from the use of new chemotherapeutic agents, as exemplified in the treatment of osteogenic sarcoma and Ewing sarcoma. Adjunctive therapy with these agents is combined with either surgical removal (osteogenic sarcoma) or radiation therapy (Ewing sarcoma) to control the primary lesion. Such treatment programs are based on two facts: (1) In osteogenic sarcoma, 80 percent or more of patients have unrecognizable microscopic metastatic lesions when they begin treatment. This figure is higher in Ewing sarcoma. Thus, the five-year survival rate before chemotherapy is only about 20 percent for osteogenic sarcoma and even lower for Ewing sarcoma. (2) Available chemotherapeutic agents destroy malignant cells with a success rate inversely proportional to the number of cells present.

The principal chemotherapeutic agents used for osteogenic sarcoma are vincristine, methotrexate, folinic acid (citrovorum factor) at times integrated with doxorubicin (Adriamycin) and, most recently, cisplatin. The agents used in Ewing sarcoma have been principally vincristine, cyclophosphamide, antinomycin-D and doxorubicin (Adriamycin).

Adjuvant chemotherapy following appropriate control of the primary lesion is associated with a projected three-year survival rate of about 60 percent in osteogenic sarcoma and over 70 percent in Ewing sarcoma.

Although it has been recognized that three rare variants of osteogenic sarcoma (periosteal, parosteal, and central osteogenic sarcoma) can be appropriately treated in some locations by local surgical resection rather than amputation, the more classic osteogenic sarcomas have always required amputation to achieve local control. The potential for destroying residual microscopic tumors has raised the possibility of resection for some classic osteogenic sarcomas if they are small and in appropriate locations. In Ewing sarcoma, local control by resection, in combination with appropriate chemotherapy, might bypass late complications of radiation therapy in growing limbs. However, these should be considered experimental approaches at present.

Jaffe's summary article (1975) describes the potential of combined modality approaches for these problems, while Taylor and colleagues point out in their report (1978) the difficulties of dependence on historical controls for assessment of new treatment programs.

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External Fixation

THE CONCEPT of external fixation has interested orthopedic surgeons for many years. Since 1853, when Malgaigne described a "claw" used percutaneously to draw together and hold the pieces of a patellar fracture, external fixation of long bones has been a means of treating fractures. Anderson (1934) and Stader (1937) attempted to fix fractures and other long-bone problems with external devices.

In 1938 Raoul Hoffman, a Swiss general surgeon and carpenter, developed the external device system bearing his name. This device has recently come into vogue in the United States because of improvements in metallurgy and modifications made by Vidal in France. External fixator devices, such as the Hoffman apparatus, have a role in the management of difficult orthopedic problems, not ordinarily treatable by traditional methods. It is particularly useful in septic nonunions and open fractures with massive soft tissue loss. It has been used with success in stabilizing severely displaced pelvic fractures, and has also been extremely useful in arthrodesis of the knee and ankle.

Applications to the upper extremities have been limited, but again when severe soft tissue and bony loss is present, the external fixator can main-

tain alignment until further tissue reconstruction can be planned. Control of a very short proximal or distal segment in fractures around the elbow and wrist have been treated with the Hoffman apparatus with surprising success. Additional devices are now available in miniature form for fixation of hand fractures.

Pin placement is critical when applying external fixators, and the devices are not without complications. However, the availability of fixators that permit immediate rigid bony fixation and alignment, without the encumbrance of circular casts or traction, have added another dimension to the rapidly expanding field of the care of the musculoskeletal system.

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Epidural Venography

THE MAJOR INDICATION for epidural venography remains a herniated intervertebral lumbar disc. Because the epidural veins lie behind the vertebral bodies and cross the intervertebral disc spaces, they are sensitive indicators of effects of extradural mass on the subarachnoid space and nerve roots in the anterior and lateral recesses of the spinal canal. This procedure is of particular value in evaluating the L5-S1 intervertebral disc space, at which site the thecal sac may not be adjacent to the anterior spinal canal wall. An added value of epidural venography is its lack of complications, in that it does not violate the intrathecal space.

The procedure is done via the femoral veins with catheterization of the presacral or ascending lumbar veins. These veins intercommunicate with the extradural veins through a valveless system. Water-soluble contrast medium is injected to visualize these veins, and is ultimately excreted through the patient's kidneys.

The normal appearance of the epidural veins is that of a "rope ladder" with the veins deviating laterally over the intervertebral disc space and coming medial to run between the pedicles of the vertebral bodies. An abnormal venogram will show either deviation and thinning of the veins at the intervertebral disc level, or total obstruction of the venous plexus. Frequently, multiple levels will be abnormal and may represent minimally symptomatic disc degeneration. Multilevel disease is often indicative of lumbar stenosis.

The reported accuracy of epidural venography is 90 percent or higher.

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Compartment Syndromes of the Leg

A COMPARTMENT SYNDROME is the result of increased tissue pressure in a closed fascial space (compartment) compromising the circulation to the nerves and muscles within the involved compartment. Of the four compartments of the leg, the anterior is the most commonly involved.

Tibial fractures or a severe contusion are the most common causes of the syndrome. However, it can be initiated by a multitude of problems, such as drug overdose with limb compression, third degree burns, arterial occlusion with postischemic swelling and vigorous exercise. The initial injury causes hemorrhage, edema, or both, in the closed fascial compartment of the extremities. As fluid accumulates, intracompartmental pressure increases, causing ischemia. A vicious cycle sets in, with the ischemia leading to increased capillary permeability and further edema in the compartment. The natural course of an untreated compartment syndrome may be devastating. The resulting muscle contracture and neural deficit are termed Volkman contracture.

The earliest finding of a compartment syndrome is swelling and a palpable tenseness over the involved compartment or compartments. Pain, especially when stretching the involved muscles, is a common symptom; however, it is somewhat difficult to quantify and is dependent on a patient's threshold of pain. Later in the course of the disease, pain may be absent because of anesthesia resulting from nerve ischemia. At times paresis (weakness) may be difficult to interpret because it may be secondary to nerve involvement, primary muscle ischemia, guarding in response to pain or a combination of all three. The most reliable physical finding is sensory deficit. In the early stages of a compartment syndrome, sensory deficit may manifest itself only as paresthesia, but with delay in therapy, anesthesia will result. Care-

ful evaluation of the sensory deficit using modalities such as pinprick and two-point discrimination are important. Except in the presence of arterial occlusion (emboli, vessel laceration or vessel injury) peripheral pulses and capillary fill are routinely *intact* in compartment syndromes. Rarely will intracompartmental pressure be high enough to occlude the major arteries traversing the compartment. The pressures are usually in the range of 30 to 70 mm of mercury. This is high enough to occlude capillaries, arterioles and veins, but not the major arteries.

In uncooperative and unreliable patients, unresponsive patients or patients with a possible nerve deficit, measurement of tissue pressure is a valuable adjunct in making the diagnosis of a compartment syndrome. We have employed the wick catheter technique as it allows direct measurement of equilibrium intramuscular pressure. Normal intramuscular pressure ranges between 0 and 8 mm of mercury. When the intramuscular pressure is greater than 33 mm of mercury, muscle and nerve damage begins to occur as observed in our clinical and laboratory experience.

The only effective means of treating a compartment syndrome is surgical decompression (fasciotomy of the involved compartments). This is simple and relatively easy, but must be done as an emergency procedure to prevent permanent muscle and nerve injury (Volkmann contracture). In patients with clinical findings as noted above and a compartment pressure greater than 30 mm of mercury, immediate fasciotomy is indicated. With early diagnosis and prompt therapy, the leg can be restored.

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EDITORIALS

Hypothermia

HYPOTHERMIA IS DEFINED as a clinical condition in which the deep body temperature falls below 35°C (95°F). As recently as 20 years ago it was thought to be a rare condition, but since the early 1960's it has become recognized as a problem particularly affecting elderly people. Hospital records have indicated that very few cases are recognized clinically before admission, but a survey carried out by the Royal College of Physicians of London[1] in ten hospitals in England and Scotland during three months in the winter of 1965 showed that 0.68 percent of all patients admitted had hypothermia. Of these, 42 percent were older than 65, and the incidence in this age group was 1.2 percent. Ten years later a further study by Goldman and her colleagues[2] showed that hypothermia occurred in 3.6 percent of all patients older than 65 who were admitted to hospital.

Many factors are responsible for the greater liability of old people to the development of hypothermia. In a population study conducted by Fox and his colleagues,[3] 10 percent of elderly people living at home were found to be on the border line of hypothermia, with a deep body temperature (as measured by urine temperature) of less than 35.5°C (95.9°F). These persons were thought to have some degree of thermoregulatory failure as shown by the inability to maintain an adequate core-peripheral temperature gradient. Further investigation of this impairment of thermoregulatory control by Collins and co-workers[4] showed that abnormal patterns of peripheral blood flow on cooling accompanied by a failure of vasoconstriction were much more common in old people than in young. When tests of thermoregulatory function were repeated four years later with the same subjects[4] a significantly higher proportion had low peripheral blood flow and a higher proportion had a nonconstrictor response on cooling. Postural hypotension with a fall in systolic pressure of 20 mm of mercury or more on standing occurred in 14 percent of old people—again an indication of impairment of autonomic function in old age. In addition, many old people have a diminished sensitivity to cold. Tests of digital thermosensation show that young people can perceive mean temperature differences of about 0.8°C whereas older persons can discriminate only between mean temperature differences of 2.1°C and some are unable to perceive temperature differences of 5.0°C or more.[4] It is likely that a lessened sensitivity to cold is one of the reasons for the relatively large number of old people who appear to be able to tolerate cold conditions without discomfort. Nevertheless, such persons may be at risk of overtaxing the heat-conserving capacity of a failing thermoregulatory system.

The common clinical conditions associated with hypothermia in the elderly are bronchopneumonia and other severe infections, cardiac infarction and pulmonary embolism, which can cause an acute derangement of thermoregulatory mechanisms. Myxedema and diabetes mellitus are the most frequent endocrine disorders causing hypothermia. In persons with diabetes, hypothermia can complicate hyperglycemic ketoacidotic coma and hyperosmolar nonketotic coma; but in elderly persons, an important factor is the presence of autonomic dysfunction associated with diabetic peripheral neuropathy. In several neurological and locomotor disorders immobility can limit the amount of heat generated, and in parkinsonism there may be an additional factor of disturbance of autonomic function. Patients with confusional states and dementia may be unaware of environmental hazards and may not adequately protect

themselves against the cold. The psychotropic drugs, especially phenothiazine tranquillizers, prescribed for these conditions may also affect thermoregulation. Some of these drugs lead to hypothermia by the abolition of shivering and by impairing the normal centrally mediated vasoconstrictor response to cold.

Acute alcohol intoxication and chronic alcoholism are well-recognized causes of hypothermia. In the series reported by Goldman and colleagues[2] alcohol was implicated in 6 of 39 elderly patients with low body temperatures admitted to hospital. These patients are often vagrants who have been subjected to cold out-of-doors. Alcohol causes hypothermia mainly by inducing vasodilatation, but it also reduces shivering and depresses central thermoregulatory control. In addition, alcohol can induce hypoglycemia, especially when taken after exercise and on an empty stomach. Haight and Keatinge[5] found that the ingestion of 28 ml of alcohol by fit young men lowered the blood glucose level to 40 mg per dl. Following exposure to cold air for half an hour the blood glucose level fell even further, and deep body temperatures dropped by 2.8°C (5°F). When alcohol ingestion was not a factor, fasting, exercise and exposure to cold affected neither the body temperature nor the blood glucose level.

In the August issue Dr. Faith Fitzgerald of the University of Michigan Medical School reported findings in 22 hypothermic patients who, with the exception of 2, were alcoholics [Fitzgerald FT: Hypoglycemia and accidental hypothermia in an alcoholic population. West J Med 133:105-107, Aug 1980]. Nine patients (41 percent) had serum glucose levels of less than 50 mg per dl. Fitzgerald emphasizes the importance of blood glucose estimation and administration of glucose intravenously in these alcoholic hypothermic patients who are found to be hypoglycemic. Philip and Smith[6] have drawn attention to the often overlooked association between hypothermia and Wernicke encephalopathy. The petechial hemorrhages that occur in the walls of the third ventricle, the hypothalamus and mammillary bodies are probably responsible for the impaired temperature regulation in this condition, which in turn is caused by a thiamine deficiency, often in association with alcoholism. If recognized early enough the response to intravenous administration of thiamine is usually dramatic.

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ACCME

IT APPEARS that the rift between the American Medical Association and the Liaison Committee on Continuing Medical Education (LCCME) has ended, and that there will now be a single body to be called the Accreditation Council for Continuing Medical Education (ACCME). This is a welcome turn of events and much credit goes to the principals concerned who simply went ahead and did what needed to be done. The new body will be relatively unfettered and it has a clear mandate from its seven sponsoring organizations to do what needs to be done for the accreditation of continuing medical education (CME).

CME is emerging as a very major segment of medical education and its dimensions are quite different from undergraduate education or residency training. Undergraduate medical education seeks to give a student a broad framework upon which to hang a growing knowledge of medicine. It generally occurs in just one kind of setting, a medical school. Residency training enables a postdoctoral student to master a specialty which may be as broad as family practice or as narrow as nuclear medicine. It may occur in one or several settings. Although it has roots in broad general medicine and in a physician's specialty, effective CME relates much more closely to the further differentiated practice of an individual physician, and is at its best when it addresses the kind of problems that a physician sees or may see in that practice. And then CME takes place in many, many kinds of settings.

Accreditation of CME is an important and complex task. There must be minimum standards and there must be accountability. Also there must be enough flexibility to take into consideration many kinds of learning in many different situations. And

accreditation of CME, like the accreditation of medical schools or residency programs, should also serve as a potent stimulus for improvement and increasing excellence. Yes, ACCME has a complex and important task, particularly in these troubled times. We wish it every success in meeting its important challenge.

—MSMW

Macroamylasemia: A Biochemical Aberration in Search of a Disease

SERENDIPITOUS DISCOVERY of a previously unappreciated clinical phenomenon is not an end in itself. Attendant upon all such disclosures are the twin obligations to assess the significance of the finding and to explain its pathogenesis. Such is the situation with respect to the peculiar aberration dubbed "macroamylasemia." And therein lies the rub.

Klonoff's review entitled "Macroamylasemia and Other Immunoglobulin-Complexed Enzyme Disorders," elsewhere in this issue, and another published by others two years earlier,[1] summarize existing information and define the current status of this disorder. Macroamylasemia, when first described,[2,3] was conceived of as the presence in circulating blood of an enzymatically active macromolecular complex. The large size of this molecule was thought to preclude its excretion in the urine by the kidneys and to result thereby in hyperamylasemia. It has now become evident, however, that this classic form (type 1) is not the sole guise in which macroamylasemia may appear. The aberration may also be found in cases of hyperamylasemia in which urinary amylase is not diminished (type 2), and even in persons with normal values for both serum and urine amylase (type 3).

Macroamylasemia is also far from the bizarre rarity of passing moment that it first seemed to be. Klonoff has accumulated 195 cases from reports that have appeared in the worldwide literature (including one case of his own). The actual number of cases that have been encountered in various laboratories around the world, however, is doubtless considerably larger than the number reported. For example, over 80 cases of type 1 macroamylasemia have been studied to date in our laboratory alone. Of these, only 20 have been systematically reported[4,5] and a few others have been discussed or referred to pari passu.

The observations of Barrows and colleagues[6] and of Helfat and co-workers[7] are especially impressive with respect to the prevalence of this alteration. They found *direct* evidence of macroamylasemia in approximately 1.5 percent of 1,052 patients with a wide variety of clinical disorders. Similarly, Klonoff estimated that the mean frequency of macroamylasemia in a series of 1,524 collected cases in which the diagnosis was based on *indirect* evidence was just over 1 percent. Of added interest with respect to the cases reported by Barrows and her associates and Helfat and his co-workers was the fact that the macroamylasemia was principally type 3. Noteworthy also were their findings that the complex may appear only transiently.

Investigative studies aimed at defining the characteristics of the macroamylase complex have made it clear that it is not homogeneous and that much more is involved than the original appellation "globulin-bound amylase"[2] would imply. Fundamentally, it consists of a normal sized amylase attached to a binding substance(s). The latter appears to consist in most cases of a variable molecular weight protein of the nature of an immunoglobulin. There is also evidence, however, suggesting that the binding substance in some instances may be a polysaccharide or glycoprotein.

The amylases of ordinary molecular weight released from macroamylase complexes susceptible to dissociation in an acid medium have been found on isoamylase analysis to be preponderantly of the salivary type (S-type).[8] Analogously, most of the binding substances isolated by gel chromatography from a group of 30 macroamylasemic sera displayed greater binding affinity for salivary than for pancreatic type (P-type) isoamylase. In one case, indeed, the substance was able to bind only S-type.[9] The explanation for this tendency and its significance remain to be elucidated. Purely as an aside, however, it is tempting to observe that if it were possible to obtain large quantities of the material noted in the one case just cited that bound only S-type isoamylase, this substance would provide an admirable means of determining the relative amounts of the principal isoamylases present in serum and urine.

Several bits of evidence suggest that macroamylasemia may be the product of an autoimmune

process: its occurrence in some patients with a so-called immune disorder; the demonstration that that binding substance in some instances is an immunoglobulin, and the dissociation of some macroamylase complexes in an acid medium (a characteristic feature of antigen-antibody complexes). Macroamylasemia has also been found, however, in otherwise healthy persons and in patients with a variety of nonimmune disorders to which the macroamylasemia has no discernible relationship. Furthermore, not all macroamylase complexes exhibit acid dissociation. Beyond this, much has yet to be learned of the nature of the binding substance(s). It would seem premature, therefore, to draw conclusions at this time concerning the autoimmune nature of the amylase macromolecule.

Caution should likewise be exercised regarding the hypothesis arising from the prevalence surveys of Barrows and colleagues[6] and Helfat and coworkers.[7] Their observation that patients with various disorders may display macroamylasemia without hyperamylasemia encouraged the suspicion that macroamylasemia may result from binding of normal amylase by a protein elaborated when bodily function is altered by disease. This suggestion that formation of a macroamylase may be a nonspecific marker of disease, however, remains to be substantiated by convincing evidence.

The principal clinical interest attaching to macroamylasemia remains the need to distinguish it from other conditions that are attended by hyperamylasemia. The possibility of macroamylasemia should especially come to mind when (1) serum amylase activity is persistently elevated without apparent cause; (2) amylase excretion into the urine is reduced, as reflected in an amylase clearance:creatinine clearance ratio of 1 percent or less, and (3) renal function is unimpaired. These indirect hallmarks of the condition, however, are not in themselves sufficient to permit a conclusive diagnosis. The very same indirect features may also be found in clinical cases of "S-type hyperamylasemia,"[10] a condition in which there is no macroamylase in the serum and in which heightened serum amylase activity results from a rise principally of S-type isoamylase. Moreover, a circulating macroamylase may be found in some cases of hyperamylasemia in which urinary amylase is not diminished (type 2) and in some persons with normal values for both serum and urine amylase (type 3). Positive identification of macroamylasemia, therefore, requires use of a test that shows directly the existence of a macroamylase molecule.

Once macroamylasemia has been identified, what are the clinical implications? Careful analysis of cases of classic type 1 macroamylasemia has failed to relate this disorder clearly to any particular disease or symptom complex.[4] Even though abdominal pain is a frequent complaint in patients with types 1 and 2 macroamylasemia, this does not establish a causal relationship between the two. Indeed, the prevalence of pain in patients discovered to have macroamylasemia probably is merely a reflection of the much greater tendency for serum amylase assay to be done in patients with abdominal pain than in those without this symptom. For the moment, therefore, macroamylasemia associated with hyperamylasemia should be viewed as a biochemical aberration without specific clinical expression in itself.

It should be emphasized that while the finding that there is a macroamylase in the serum tends to exonerate pancreatic disease as the basis for the elevated serum amylase activity, it does not in itself absolutely exclude the possibility of concomitant pancreatitis. Both conditions have on occasion been found to coexist. One way of establishing that both disorders are present is to prove the presence of a circulating macroamylase by a *direct* test, and to show that P-type isoamylase is elevated above the upper limit of normal by means of isoenzyme analysis of the ordinary size amylase present in the same serum.

Macroamylasemia, originally thought to be a bizarre and probably exotic disorder, has emerged as an alteration of surprising frequency and unsuspected complexity. Clinically, however, it remains principally a biochemical aberration in search of a disease.

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Caveat Medicus

We are now being told that there will be a surplus or even a surfeit of doctors by 1990, which is only ten years hence. Leaving aside such debatable questions as whether the assumptions are correct or not, or how reasonable are the conclusions drawn from the assumptions, or whether there are too many specialists or too few primary care physicians, or whether the problem is really a need for a better geographic distribution of physicians, there are some related trends that should also concern the medical profession as their numbers increase.

Several things seem to have been happening more or less at the same time. Medical science has begun what is sure to be an ever-increasing capacity for rendering more effective medical care and our educational system has been producing large numbers of physicians superbly trained in the technology of this more effective care. But at the same time society has been gradually legitimatizing other health professionals for patient care and increasing the allowable scope of their practice. Much that formerly could only be done by physicians can now be done by other health professionals who are less well trained. Other systems such as osteopathy and chiropractic are gaining greater acceptance with growing public support, and now holistic healers of various kinds are upon the scene and are attracting patients who for one reason or another have been either dissatisfied or unsatisfied with their medical care. And finally, many patients are simply treating themselves, especially if the ailments are minor. Thus, at the same time the number of physicians is to increase substantially, their near monopoly in medical care is being seriously eroded, if indeed it has not already been broken. Both seem certain to have as yet unpredictable effects on medical care, on the consumer or purchaser of medical care, and on physicians.

One can begin to see some of the fallout from all of this in a few areas where the physician-to-population ratio already is exceptionally high. Quite suddenly it may become apparent that there are just not enough patients around to consume all of the superb technologic care that the available physicians are prepared to deliver and, not surprisingly, the realization of this can create something almost approaching panic among the practicing profession.

Caveat medicus! It seems likely that as more physicians are trained to give more expensive and more highly technologic care, the relative if not absolute number of patients seeking or needing this care may be declining. It is probable that more patients may actually need caring than need curing in order to feel better, and it seems at least possible that the caring function, which was so much a part of traditional medicine, may now be slipping into the hands of other practitioners who may be perceived as more effective in helping many patients to feel better.

Let physicians beware. If physicians become just technicians, even superb ones who do miraculous things, it may be at the cost of surrendering that large body of patients who are feeling poorly, but not in need of high technology, to other persons who take the time and take the trouble to help these patients to feel better. This traditionally has been a principal function and a high privilege for physicians. It should not be surrendered to others. But perhaps all is not lost. Perhaps as their numbers increase more physicians will soon have more time to spend with more patients—caring for them and also protecting their share of the trade.

—MSMW

Do You Have *Salmonella* in Your Future?

Elsewhere in this issue is a Specialty Conference on salmonellosis.

Although studies of the salmonellae date back 100 years, much remains to be learned about these important pathogens of humans. This editorial deals briefly with new aspects of the epidemiology, diagnosis, treatment and prevention of typhoid fever, which is becoming uncommon in

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the United States, and indicates some gaps in our understanding of the epidemiology, treatment and prevention of nontyphoidal *Salmonella* infections, which are becoming more common.

The epidemiologic characteristics of typhoid fever in the United States are gradually changing. Domestically acquired cases are becoming less common, and the number of typhoid cases acquired abroad now exceeds the number acquired in this country. Mexico and the Indian subcontinent were the most frequently reported locales for foreign exposure.[1] Although laboratory-acquired typhoid fever has been long recognized, 11 percent of the sporadic cases reported in the United States were recently attributed to laboratory exposure.[2] Most persons with laboratory-acquired cases became infected following voluntary exposure to the organisms, such as in teaching or proficiency testing exercises.

Examination of urine specimens for Vi and other *Salmonella typhi* antigens using a slide coagglutination technique has been shown recently to be a sensitive test for diagnosing typhoid fever.[3] These urine screens were much more specific for diagnosing typhoid than the serum agglutination assays for O and H antigens. This new technique may be of particular value in those instances when a patient has received antibiotic therapy previously and cultures, therefore, may be negative. In addition it offers a serological technique that does not require paired specimens.

Fecal cultures to detect chronic carriers may be insensitive measures of the excretion of *S typhi* because excretion can be intermittent. Serological tests can be useful in screening suspected carriers to suggest where persistent efforts at culturing are worthwhile. A new assay to detect Vi antigen in serum is as sensitive but more specific than the commonly used Vi test for detection of chronic carriers.[4] This test has been able to detect resolution of the carrier state as well.

Although chloramphenicol has been the mainstay of chemotherapy for typhoid for 30 years, trimethoprim-sulfamethoxazole appears to be as effective.[5] The epidemic in Mexico of illness due to chloramphenicol-resistant *S typhi* has now abated[6]; however, chloramphenicol-resistant strains occasionally appear from South and Southeast Asia. For patients returning from areas where chloramphenicol-resistant strains exist, initial treatment with trimethoprim-sulfamethoxazole should be considered while awaiting results of susceptibility testing.

The mainstay of treatment for chronic typhoid carriers has been cholecystectomy with concurrent antibiotic drug therapy. Although many antimicrobial agents have been tried to effect a medical rather than a surgical cure, ampicillin has been the most effective. However, results of ampicillin therapy have been disappointing, largely due to poor patient tolerance to long-term, high-dose administration of the drug. Amoxicillin, an agent to which *S typhi* is more sensitive in vitro and which is better absorbed from the gastrointestinal tract after oral administration than ampicillin, now appears to be superior for eradication of the carrier state. In a recent series using amoxicillin, Nolan and White[7] cured nine of ten patients able to take the full four-week regimen but only two of five taking a shorter course of medication; cure was associated with high serum levels of amoxicillin. Three carriers who had gallstones were cured with amoxicillin.

The development of mutant avirulent strains of *S typhi* raises the possibility that a live vaccine may be a reality before the end of the decade. In a preliminary study of the efficacy of the epimeraseless strain as an orally given vaccine, only 7 percent of vaccinated volunteers versus 53 percent of unvaccinated volunteers became ill when challenged with 10^5 virulent *S typhi* organisms.[8] In contrast to the local and systemic reactions that often accompany cutaneously administered killed vaccine, side effects from the live vaccine were mild. This vaccine is being studied in areas where typhoid is endemic.

There is still much to be learned about how to interpret the data collected by the *Salmonella* surveillance system in the United States.[9] The number of reported isolates underestimates the number of infections, and the distribution of infections by age and by serotype is probably skewed by over-sampling of the seriously ill and the extremes of age. Although most of the reported vehicles are identified in investigations of large outbreaks occurring outside the home,[10] most reported isolates are not clearly associated with large outbreaks and probably result from exposure in the home. The foods that are associated with salmonellosis, whether eaten at home or in restaurants, may have been cross-contaminated, so that the foods that bring *Salmonella* into the environment may not always be clearly identified by food histories. For example, the investigation of the first recognized outbreak of *S agona* infection implicated cole slaw as the vehicle at a restaurant.

However, cross-contamination had occurred on a common cutting board used for the cole slaw and for poultry; the poultry had been fed *S agona*-contaminated Peruvian fish meal.[11] Although animal products used as foods are the major reservoir of the *Salmonella* organisms that infect humans, not all human infections result from direct ingestion of contaminated foods. Person-to-person spread can occur, though this type of transmission is most often reported from institutions,[12] particularly if the index case patient is an infant.[13] Nontyphoid *Salmonella* isolates, which are investigated far more frequently in laboratories than is typhoid, may transform a laboratory into a *Salmonella* reservoir, from which infections of laboratory workers may occur. More data are needed on this subject.

There is much to be learned from studying data concerning individual *Salmonella* serotypes. Sometimes serotypes and vehicles travel together, such as *S dublin* and unpasteurized milk,[14] and *S urbana, S litchfield* and *S java* and turtles.[15] Some serotypes have distinctive geographic distributions, unexplained by known vehicles or modes of spread. Between 1970 and 1976, *S javiana* isolates made up a much higher percentage of the total number of *Salmonella* isolates in Florida (11.2 percent), Arkansas (9.0 percent), Texas (8.3 percent) and Georgia (3.9 percent) than they did in the United States as a whole (1.9 percent). More than 95 percent of isolates of *S weltevreden* are from Hawaii. In addition to distinctive geographic distributions, striking variations in the median age of persons from whom *Salmonella* serotypes have been isolated suggest that they have different vehicles or different characteristics of transmission. For example, the median age of persons from whom *S gaminara* and *S rubislaw* are isolated is less than 9 months, while the median age of persons from whom *S cholerae-suis* and *S dublin* are obtained is greater than 40 years.[16] *S newport* was isolated from persons with a low median age in the American South and a high median age in the North. Occurrence of *S newport* does not appear to be related to season in the Northeast, although it is highly seasonal in the South. Some *Salmonella* serotypes have appeared in scattered locations throughout the country and never become a major problem, while others have become important causes of human illness. *S agona,* a rare serotype in 1970, entered several countries in poultry feed and is now a common human isolate in some of them. *S hadar,* once rare in humans, is now common in the United Kingdom,[17] is becoming important in Canada and is being found with increasing frequency in this country. *S hadar* appears to have been amplified by establishment in a single turkey farm and then disseminated by movement of infected turkeys. In Britain[18] and other European countries, phage typing of *S typhimurium* has allowed study of the spread of clones of *S typhimurium* throughout a country or from one country to another.

Although it has been stated repeatedly that human salmonellosis requires a large dose of organisms to infect and cause illness, few data are available concerning the ingestion of small doses. No data are available on whether a small dose might be infective in a specific vehicle. There are data that show that small doses were infective in chocolate[19] and in water.[20] It may be important to consider not the ID_{50} (infective dose for 50 percent), which can be as large as the volunteer studies suggest,[21] but to consider the ID_1 (infective dose for 1 percent), which can be the dose frequently encountered in some situations. Variations depending on dose, vehicle and serotype might help explain how it is that many people become exposed, some become infected and few become ill, producing what we call "sporadic" cases.

Although it is frequently stated that human salmonellosis in infants is associated with high frequency of bacteremia,[22] there are few data to substantiate this suggestion. The more seriously ill infants are brought to the attention of physicians, and those with high fevers are more likely to have specimens cultured, so the true frequency of bacteremia in children with *Salmonella* infection is unknown. Whether therapy is essential for the treatment of all infants with salmonellosis or for those younger than 3 or 6 months of age, is still a matter requiring more data. In any instance in which treatment is considered, the common occurrence of multiple-antibiotic resistance limits the choice of useful drugs.

Difficulties occur because of prolonged enteric carriage even with nontyphoid salmonellosis, although carriage for more than a year is rare. When an infant is infected and enteric carriage is prolonged, it is difficult to return the infant to a day-care center, and it is uncertain what risk occurs in the family when members are exposed to this infant. Similarly, prolonged carriage in food handlers, nurses or laboratory workers may cause

significant economic dislocation for the affected person. More data are needed about how to treat these instances of prolonged excretion.

To reduce the chances of *Salmonella* in our future, efforts must be made to control *Salmonella* infections in the principal reservoir, domesticated animals. Antibiotic resistance is now common in salmonellae isolated from humans,[23] perhaps related to the use of antibiotic drugs in animal husbandry. To reduce the frequency of antibiotic resistance transferring from enteric bacteria of animals to those of humans, the unnecessary use of antibiotic drugs in animals must be controlled. Because of the high cost of human salmonellosis,[24] in morbidity, mortality and dollars, physicians must take a leading role in urging control of *Salmonella* infections in animals combined with control of unnecessary use of antibiotic drugs in animal feeds.

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CASE REPORTS

Refer to: Marini JJ, Shearn WE: Lobar consolidation and hemorrhagic bronchitis in chronic eosinophilic pneumonia. West J Med 133:439-441, Nov 1980

Lobar Consolidation and Hemorrhagic Bronchitis in Chronic Eosinophilic Pneumonia

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SINCE ITS INITIAL DESCRIPTION, chronic eosinophilic pneumonia has been defined as a disease of lung parenchyma that is recognized by a characteristic clinical history and a roentgenographic pattern of scattered nonsegmental peripheral infiltrates.[1-4] It has been emphasized recently that these features are sufficiently specific to allow definitive diagnosis without the necessity of lung biopsy in most instances.[3,4] In this report we describe a patient with combined eosinophilic pneumonia and bronchitis whose atypical presentation resulted in diagnostic confusion and delay of appropriate therapy.

Report of a Case

A 46-year-old woman who did not smoke was admitted with complaints of progressive dyspnea and hemoptysis. Her past medical history was notable only for menorrhagia secondary to biopsy-proved chronic endometritis. Six weeks before we saw her, a persistent nonproductive cough, anorexia and fatigue had developed. Two weeks before admission to our facility, she was admitted to another hospital with complaints of hectic fever, night sweats, mild dyspnea and weight loss of 7 kg. She had no history of asthma, atopy or the use of any medicine. A chest radiograph (Figure 1) showed right upper lobe consolidation and was interpreted as compatible with lobar pneumonia. Stain and culture of the sputum did not identify bacterial, fungal or mycobacterial pathogens. The total leukocyte count was 11,500 per cu mm with 5 percent eosinophils, and the hemoglobin value was 9.6 grams per dl. Erythromycin therapy (250 mg four times a day) was begun, but the patient experienced little subjective improvement. No rectal temperature exceeding 38.9°C (102°F) was recorded, and she was discharged on the third hospital day with presumptive diagnoses of bacterial or mycoplasmal pneumonia and iron deficiency anemia caused by menstrual blood loss.

Ten days later she was admitted to our hospital because of progression of symptoms despite antibiotic therapy. She appeared cachectic, diaphoretic and dyspneic at rest. Her vital signs were oral temperature 39.4°C (102.9°F), respirations 32 per minute, pulse rate 96 per minute, and blood pressure 100/60 mm of mercury. Tubular breath sounds were heard bilaterally over the upper lung zones, and no wheezes were detected. The remainder of the physical examination was unremarkable.

The chest roentgenogram (Figure 2) showed extension of the original infiltrate to involve the peripheral regions of the upper and middle lung zones, bilaterally, with sparing of central areas. Abnormal laboratory values included: hemoglobin 8.1 grams per dl, leukocytes 15,500 per cu mm with an absolute eosinophil count of 910 per cu mm, albumin 2.1 grams per dl and erythrocyte sedimentation rate (Westergren) 95 mm per hour. Blood film and erythrocyte indices indicated hypochromia and microcytosis. The test for serum creatinine was 1.0 mg per dl, and analysis of urine was unremarkable. Sputum was blood-tinged and contained numerous segmented cells but scant flora; a Wright stain for eosinophils was not done. Skin tests with tuberculin, mumps and *Candida* antigens were nonreactive. Stool and sputum examinations for ova and parasites and serum tests for antinuclear antibodies and rheumatoid factor were negative. Assay for total hemolytic complement ($C'H_{50}$) was within expected normal values.

The patient's total lung capacity and single breath diffusing capacity for carbon monoxide were 34 percent and 48 percent of the predicted

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values, respectively. No airflow obstruction was detected using a spirometer. Arterial blood gas values while breathing room air were: pH 7.50, Po_2 59 torr, and Pco_2 34 torr.

Because of the patient's radiographic and clinical features, the differential diagnoses considered were tuberculosis, partially treated bacterial pneumonitis and eosinophilic pneumonia. Following discontinuation of antibiotic drugs, blood and sputum cultures were obtained, antituberculous therapy was begun and three units of packed erythrocytes were given. Because her diagnosis continued to be uncertain, fiberoptic bronchoscopy was carried out on the fourth hospital day. All passages were widely patent to the subsegmental level, but diffuse hemorrhagic bronchitis involved both central and peripheral airways. Multiple endobronchial biopsy specimens were obtained from the right main bronchus and transbronchial specimens were obtained from the right upper lobe.

Figure 1.—Initial chest roentgenogram, showing consolidation of the right upper lobe.

Figure 2.—Chest roentgenogram taken during second hospital stay, showing widespread peripheral infiltrates with central zone sparing characteristic of chronic eosinophilic pneumonia.

Histopathologic findings were those described for chronic eosinophilic pneumonia.[1,2] The biopsy specimen of pulmonary parenchyma (Figure 3A) showed alveolar and interstitial filling with histiocytes, lymphocytes, fibroblasts and eosinophils. Scattered neutrophils and giant cells were identified. The bronchial mucosa (Figure 3B) was thickened by a similar infiltrate of eosinophils and histiocytes. No bacterial, fungal or acid-fast organisms were detected when the mucosa was stained or cultured. Acute and convalescent titers for cold agglutinins and serum antibodies to mycoplasma pneumoniae, legionella pneumophila, influenza A and B, adenovirus, chlamydia and

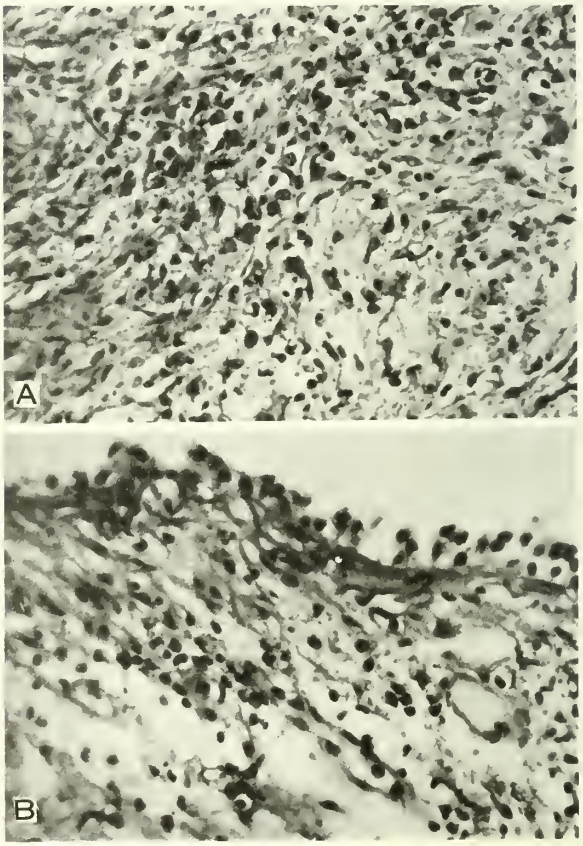

Figure 3.—Biopsy specimens of pulmonary parenchyma **(upper panel, A)** and of mucosa from a central bronchus **(lower panel, B).** An infiltrate of eosinophils and hisitocytes is present in both specimens. (Hematoxylin-eosin stain, original magnification ×400.)

respiratory syncytial virus were all less than 1:16. No rise in titer between samples was observed for any organism.

Therapy with 60 mg of prednisone per day was begun, and 36 hours later the patient's constitutional symptoms had improved substantially. Dyspnea rapidly diminished, and there were no further episodes of hemoptysis. A chest roentgenogram showed convincing clearing by the sixth day of corticosteroid treatment. The patient was discharged to her home on the 14th hospital day to continue prednisone and iron sulfate therapy. Subsequently, findings on a chest roentgenogram as well as erythrocyte sedimentation rate, hemoglobin and eosinophil counts returned to normal; all pulmonary function abnormalities reversed as well. Three months following discharge, the patient was still asymptomatic on low-dose alternate-day corticosteroid therapy.

Discussion

Previous descriptions of chronic eosinophilic pneumonia have urged recognition of a distinctive radiographic and clinical entity.[1,3,5] The present case illustrates that this disease may also present atypically with isolated lobar consolidation and hemorrhagic bronchitis.

In the original report of Carrington and his associates[1] three radiographic features were observed uniformly: dense nonsegmental peripheral infiltrates with sparing of central zones ("photographic negative of pulmonary edema"), rapid resolution on corticosteroid therapy and recurrence of the lesions in the same location during relapse. These points have been supported in more current literature by the observations of numerous authors.[2-11] In separate reviews, Dines,[5] Angelillo,[10] Gaensler[3] and Leitch[12] and their colleagues recently called attention to the importance of the characteristic chest roentgenogram, and on this basis cogently argued that the diagnosis is secure without tissue documentation in the great majority of cases in which the features are stereotypic. It is also important to emphasize that atypical presentations occur; radiographs that do not conform to the standard pattern have been described.[3] However, a roughly segmental distribution has been reported in only two previous instances,[11,13] and isolated lobar consolidation, as observed initially in our patient, has not been described previously.

Unlike other diseases of pulmonary eosinophilia, there is an almost complete lack of histological information concerning the conducting airways in chronic eosinophilic pneumonia. Cough and sputum production are frequent complaints, but to our knowledge the present case is the first in which diffuse eosinophilic bronchitis has been documented. Similarly, hemoptysis is recognized to occur in this disease, but little attention has been directed toward defining its site of origin. In their pathological description of eosinophilic pneumonia, Liebow and Carrington[2] showed hemosiderin-laden alveolar macrophages in a single instance in which hemoptysis occurred, and a parenchymal bleeding source was implied. Our observations in this patient indicate that the inflammatory process occasionally extends to involve the proximal airways, and that hemorrhage is a potential consequence of that involvement.

Despite its extraordinary response to appropriate therapy, eosinophilic pneumonia is potentially life threatening if unrecognized. While usually identifiable by a distinctive presentation, this disease is not confined to a unique syndrome and deserves diagnostic consideration even in cases in which highly atypical features are seen.

Summary

Isolated lobar infiltrates and hemoptysis characterized the condition of a 46-year-old woman with a subacute illness. Based on subsequent radiographs and parenchymal biopsy specimens, the diagnosis of chronic eosinophilic pneumonia was established. Despite its usual description as a parenchymal disease with a distinctive roentgenographic pattern, the atypical features of endobronchial involvement and segmental consolidation seen in this patient are consistent with this diagnosis.

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Massive Left Ventricular Mural Thrombosis With Consumption Coagulopathy in Congestive Heart Failure

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THE SYNDROME OF consumption coagulopathy occurs in association with a wide variety of underlying illnesses. In general, resolution of the coagulopathy accompanies successful treatment of the primary disorder. If the underlying pathological process is not clinically apparent, evidence of consumption coagulopathy may be a clue leading to diagnosis and appropriate therapy. Such conditions may include complications of pregnancy (for example, amnionitis or abruptio placentae), arterial aneurysms, giant hemangiomata and malignant lesions.[1]

The association of consumption coagulopathy with congestive heart failure is not widely recognized. We report a case of massive left ventricular mural thrombosis and consumption coagulopathy in the setting of congestive cardiomyopathy, and discuss the possibility that the coagulation defects that may occur in heart failure can contribute to the development of mural thrombi.

Report of a Case

A 55-year-old man was admitted to hospital with nausea and epigastric pain of four weeks' duration. There was a past history of maturity-onset diabetes mellitus, a stroke five years before the present admission, a second stroke four years before and a myocardial infarction three years previously. At the time of admission the patient was in no physical distress. Blood pressure was 160/110 mm of mercury, pulse 84 beats per minute, and respiratory rate 18 per minute; no fever was present. Carotid pulses were decreased and a right carotid bruit was present. Jugular venous pressure could not be estimated. Fundoscopic examination showed advanced diabetic retinopathy. Rales were heard in the lower third of both hemithoraces posteriorly; expiratory wheezes were scattered throughout both lungs. Examination of the heart showed a diffuse apical impulse displaced to the left, a loud second heart sound and an S4 gallop. There was mild diffuse abdominal tenderness, most prominent in the right upper quadrant. The liver was not palpable. Neurological examination showed mild spastic paraparesis of the right upper and left lower extremities and a left central seventh nerve palsy. These were stable deficits from the two previous strokes.

Results of laboratory studies done at admission included normal complete blood count, prothrombin time, activated partial thromboplastin time and routine tests of liver function. Glucose level was 249 mg per dl. A roentgenogram of the chest showed mild cardiomegaly and an electrocardiogram showed a remote inferior myocardial infarction, unchanged from previous examinations.

The patient was treated with bed rest and antacid agents, with some improvement in his abdominal pain until the third hospital day when he became lethargic and dyspneic. A new S3 gallop and more prominent rales were noted. Extremities were mottled and oliguria developed. Twelve hours later the oral temperature rose to 38.2°C (100.8°F) and increased abdominal pain and tenderness developed. After specimens for microbial cultures were obtained, gentamicin and chloramphenicol were administered. These cultures subsequently failed to show any microorganisms.

Laboratory studies carried out on the third hospital day gave these values: arterial oxygen pressure (Pa_{O_2}) 90 mm of mercury (fraction of inspired oxygen [FIO_2] 0.21), arterial carbon dioxide pressure (Pa_{CO_2}) 20 mm of mercury, pH 7.37, bicarbonate 11.7 mEq per liter; acetone determination was negative. The platelet count was 30,000 per μl, hematocrit 49 percent and leukocyte count 13,700 per μl. The prothrombin time was 42.4 seconds (control 12 seconds), activated partial thromboplastin time greater than 150 seconds (control 34.7 seconds), fibrinogen

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40 mg per dl (normal 275 to 400), and fibrin degradation products 640 μg per ml (normal <5). A peripheral blood smear showed microangiopathic erythrocyte damage with numerous fragmented forms.

A Swan-Ganz catheter was placed. The right atrial pressure was 18 mm of mercury; pulmonary artery pressure, 90/40 mm of mercury; pulmonary capillary wedge pressure, 40 mm of mercury. The cardiac index was 14 liters per minute per sq m.

The patient was treated with furosemide and nitroprusside with some hemodynamic improvement, but died 36 hours later due to progressive cardiac failure.

Examination at autopsy showed cardiomegaly (600 grams), right- and left-sided ventricular hypertrophy, and coronary atherosclerosis. A massive mural thrombus was present in the left ventricle, filling approximately 50 percent of the chamber volume. By microscopic examination, the thrombus was heterogeneous. It was well organized at its site of attachment to the endocardium. It varied from "acute" to organizing to well organized in other areas, with the most well-organized thrombus present in the apex of the left ventricle. There was evidence of antemortem thrombus attached to the left ventricular endocardium from the apex to midway between the midportion and the base of the left ventricle. There was no evidence of acute myocardial infarction.

Discussion

The abrupt development of prolonged prothrombin and activated partial thromboplastin times, elevated fibrin degradation products, decreased plasma fibrinogen concentration, thrombocytopenia and erythrocyte fragments in the circulation is convincing evidence that a consumption coagulopathy was present in our patient. The detection of widespread microthrombi in the small vessels of various organs may be taken as final proof that disseminated intravascular coagulation (DIC) is responsible for such a coagulopathy. However, lack of pathological evidence of microthrombi, as in the present case, does not exclude the occurrence of DIC. In fact, pathological evidence of DIC in humans is difficult to find.[2,3] Even in experimental models of DIC induced by intravenous injection of thromboplastic material, generally no thrombi are detected in histological studies of sacrificed animals unless the increased fibrinolytic activity is blocked by a fibrinolytic inhibitor.[4] This suggests that there is dynamic equilibrium between thrombosis and fibrinolysis and that as new thrombi are formed, they are rapidly lysed. This may explain the frequent lack of pathological findings at autopsy. From the data available, it is not clear whether the present case represents an example of disseminated or local intravascular coagulation.

It is likely that the consumption coagulopathy in this patient was due to his severe heart failure, with compensated metabolic acidosis due to decreased cardiac output and tissue perfusion. The patient's presenting complaints were probably related to hepatic and mesenteric vascular congestion due to right-sided heart failure. No other predisposing disorders were identified either clinically or at autopsy.

The association of large intravascular thrombus formation and consumption coagulopathy has been noted in a few instances with arterial aneurysms, with or without dissection or rupture,[5,6] and with massive venous thrombosis.[7] A syndrome of DIC and vegetative cardiac thrombosis has been reported in critically ill neonates, most of whom had the respiratory distress syndrome.[8] However, the cardiac and vascular lesions in these patients were platelet thrombi, with little or no fibrin deposition, and were multiple and small in contrast to the large fibrin thrombus seen in the present case. A single case of mitral stenosis, giant left atrial thrombus and consumption coagulopathy has been reported.[9] In this case, the thrombus was shown by iodine 125 fibrinogen scanning; histopathologic material was not available. The patient was treated with warfarin and acetylsalicylic acid with favorable results.

To our knowledge, the association of massive left ventricular mural thrombosis and consumption coagulopathy has not been reported previously. The syndrome of DIC must be an uncommon concomitant of congestive heart failure or mural thrombosis because this association is not generally recognized in spite of the fact that both are relatively common disorders.

Congestive heart failure and mural thrombosis had been present in our patient for some time before he entered the hospital. The most likely sequence of events was that congestive heart failure allowed development and gradual enlargement of the mural thrombus until its size and position interfered with chamber filling or ejection. At that point, rapid progression of heart failure and con-

sumption coagulopathy occurred, the latter contributing to the growth of the thrombus and, therefore, to worsening of the heart failure.

The precise processes by which the defibrination disorders are induced are only partially understood. However, some factors that can be present in a low cardiac output state such as regional tissue ischemia, stagnant blood flow, increased endogenous alpha-adrenergic activity and hepatic dysfunction may predispose a patient such as ours to the development of consumption coagulopathy.[10,11]

To what extent the coagulation disorder contributed to this patient's death is uncertain. From the findings at autopsy, however, it was clear that the bulk of the left ventricular thrombus developed acutely. Death was due to severe left ventricular failure with pulmonary edema and low cardiac output, at least partially due to compromise of the left ventricular chamber volume by the massive mural thrombus. Early administration of heparin may have been beneficial in preventing the growth of the mural thrombus. A noninvasive diagnosis before the patient died may have been possible by means of iodine 125 fibrinogen scanning or cross-sectional echocardiography.[12] The recognition that a consumption coagulopathy may occur in association with the development of mural thrombi in patients with congestive heart failure may lead to earlier diagnosis and more definitive therapy.

Summary

The association of congestive heart failure, cardiac mural thrombosis and consumption coagulopathy is not generally recognized. A case of consumption coagulopathy in the setting of congestive heart failure and massive left ventricular mural thrombosis is described. A 55-year-old man was admitted to hospital with symptoms resulting from congestive heart failure. Abrupt deterioration in his hemodynamic status was associated with development of consumption coagulopathy and rapid enlargement of a left ventricular mural thrombus, noted only at postmortem examination. Possible pathophysiologic mechanisms are discussed. Recognition that consumption coagulopathy can occur in this setting may allow earlier diagnosis and definitive anticoagulant therapy of mural thrombosis in congestive heart failure.

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Refer to: Hubbell FA, Weber MA, Megaffin BB, et al: Acute renal impairment produced by a uricosuric diuretic. West J Med 133:444-446, Nov 1980

Acute Reversible Renal Impairment Produced by a Uricosuric Diuretic

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TICRYNAFEN (2, 3-dichloro-4-[2-thienylcarbonyl]-phenoxy-acetic acid) is a uricosuric diuretic that lowers blood pressure by a mechanism similar to that of thiazide diuretics. A theoretical advantage of uricosuric diuretics is their ability to reduce rather than elevate serum uric acid levels. Although ticrynafen was recently withdrawn from general use by its manufacturer for evaluation of possible hepatotoxicity, experience with uricosuric compounds may have relevance for future therapeutic strategies. In this report we discuss two cases in which there were abrupt increases in

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Submitted, revised, March 6, 1980.

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blood urea nitrogen and creatinine concentrations soon after the institution of ticrynafen therapy.

Reports of Cases

PATIENT 1. A 66-year-old white man had a four-year history of essential hypertension controlled by hydrochlorothiazide (100 mg a day) and clonidine (0.4 mg a day). There was no history of renal, hepatic or cardiac disease. Findings on physical examination were unremarkable except for early nonexudative fundoscopic changes. Three weeks after cessation of all medications he was given ticrynafen (250 mg a day) and instructed to drink as much liquid as possible for the first three days of therapy. Blood pressure without treatment was 151/97 mm of mercury with the patient lying down and 159/101 mm of mercury standing. The blood urea nitrogen value was 20 mg per dl, the serum creatinine level was 1.1 mg per dl and creatinine clearance was 75 ml per minute. The serum uric acid concentration was 8.2 mg per dl.

After one week of ticrynafen therapy the patient was asymptomatic. The blood pressure was 154/89 mm of mercury when lying down and 158/99 mm of mercury standing. The remainder of the physical examination findings, except for the fundoscopic changes mentioned above, were normal. However, the blood urea nitrogen value had risen to 40 mg per dl, the creatinine level had increased to 2.6 mg per dl and creatinine clearance had fallen to 37 ml per minute. The serum uric acid had fallen to 5.3 mg per dl and the fractional excretion of urate had increased from a baseline of 4 percent to 19 percent. Analysis of urine showed no abnormalities and the 24-hour urine volume was 2,025 ml. There was no eosinophilia. Ticrynafen therapy was discontinued and after three months the patient's blood urea nitrogen and creatinine values returned to baseline (see Table 1).

PATIENT 2. A 49-year-old white man had a 20-year history of hypertension which was being treated with hydrochlorothiazide (50 mg a day), triamterene (100 mg a day), prazosin (2 mg a day) and metoprolol (100 mg a day). Because of an elevation in the serum uric acid concentration, administration of hydrochlorothiazide and triamterene was discontinued and therapy with ticrynafen (250 mg a day) was begun. The patient took his last triamterene and hydrochlorothiazide doses 12 hours before taking the first ticrynafen tablet.

TABLE 1.—*Values for Blood Urea Nitrogen, Serum Creatinine and Uric Acid Concentrations in Two Hypertensive Patients Before, During and After Treatment With Ticrynafen*

	Blood Urea Nitrogen mg/dl	*Creatinine mg/dl*	*Serum Uric Acid mg/dl*
Patient 1			
Pretreatment	20	1.1	8.2
During treatment	40	2.6	5.3
Posttreatment	18	1.1	6.8
Patient 2			
Pretreatment	22	0.9	9.2
During treatment	53	3.8	6.8
Posttreatment	25	1.6	8.2

One week after the institution of ticrynafen therapy the patient complained of general malaise, dry mouth and excessive thirst. Blood pressure was 146/94 mm of mercury lying down and 140/98 mm of mercury standing. The remainder of the physical examination showed no abnormalities. On the previous regimen of diuretics, the blood urea nitrogen value was 22 mg, creatinine was 0.9 mg and serum uric acid was 9.2 mg per dl. After ticrynafen therapy, the blood urea nitrogen level was 53 mg, creatinine was 3.8 mg and serum uric acid was 6.8 mg per dl. Analysis of urine showed no abnormalities and there was no eosinophilia. Three weeks after discontinuation of ticrynafen administration, the blood urea nitrogen value had fallen to 25 mg and creatinine to 1.6 mg per dl; the serum uric acid concentration was 8.2 mg per dl (see Table 1).

Comment

Ticrynafen is a diuretic that, before its withdrawal from general use, appeared appropriate for treating patients with concurrent hypertension and hyperuricemia. The blood pressure lowering effect of the drug is comparable to that of hydrochlorothiazide[1] and chlorthalidone.[2] In addition, the agent inhibits tubular reabsorption of both filtered and secreted urate[3] and thus lowers serum uric acid levels. Adverse effects seen with the use of ticrynafen include occasional weakness, faintness and lethargy. As with other diuretics, postural dizziness can occur.

The two cases presented above illustrate a potentially important adverse reaction that can occur with ticrynafen. One patient was taking a combination of hydrochlorothiazide and triamterene before the institution of ticrynafen therapy. In unpublished studies the combination of ticry-

nafen with the potassium-sparing diuretic triamterene caused an elevation of blood urea nitrogen and serum creatinine up to levels of 81 mg per dl and 5.2 mg per dl, respectively, in three of seven normal volunteers within three days of starting therapy. Although our patient did not take the two drugs concomitantly, the previous triamterene therapy probably played a major role in the abrupt increase in blood urea nitrogen values. There is no obvious explanation for the acute deterioration in renal function associated with ticrynafen in our other patient who had been without treatment for three weeks previously.

The mechanism of the renal impairment induced by ticrynafen is not known. Acute increases in uric acid concentrations in the renal tubule or uric acid-induced interstitial nephritis, although rare,[4] are possible explanations. Fortunately, these apparent reductions in renal function appear to be reversible.

Two additional cases of acute renal failure during ticrynafen treatment have recently been reported.[5,6] In both instances, ticrynafen was substituted for hydrochlorothiazide in the absence of a diuretic-free period for the purpose of rehydration. Clearly, it would be helpful for any previous diuretic treatment to be stopped at least three days before the institution of uricosuric therapy so as to allow sufficient rehydration to minimize the possibility of urate precipitation. Moreover, the future use of uricosuric diuretics should be restricted to hypertensive patients known to be susceptible to clinical gout; administration of these agents for asymptomatic hyperuricemia does not appear to be justified.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Treatment of Heat Stroke at Parkland Memorial Hospital

To the Editor: I would like to respond to the correspondence entitled "Treatment of Heat Stroke" in the September issue.[1]

The author, Dr. Farrell, noted that "Recently on the CBS Evening News, a heat-stroke victim was shown being given the recommended ice treatment at a famous Dallas hospital affiliated with a distinguished school." (It was, in fact Parkland Memorial Hospital in Dallas.) Dr. Farrell then stated that the external application of ice is the wrong treatment for heat stroke. He points out that by its vasoconstrictive effect on skin arterioles, it may actually interfere with the normal process of heat loss through the skin and that evaporative cooling should be considered as a better alternative.[2] He further went on to say that, first, one should treat the hypovolemic shock and the associated electrolyte deficiencies and imbalances, and, second, lay the naked patient on a rubber or plastic sheet, wrap him in another of cotton continually doused with water and use fans to hasten the process of evaporation.

Coming from Parkland, an institution that has produced no less than 15 authoritative papers on the pathophysiology and treatment of environmental heat illness, I would like to make a few comments and recommend three of the more comprehensive reviews from this institution.[3-5] First, I disagree with Dr. Farrell's sequence of events in the treatment of heat stroke. Hypotension which may occur as a result of the pronounced peripheral vasodilatation during hyperpyrexia, will often respond to cooling alone. If such a patient receives large quantities of saline or plasma expanders while he is hyperthermic, subsequent cooling and peripheral vasoconstriction may overload the central circulation and produce acute pulmonary edema. On the other hand, if hypotension persists after cooling, appropriate agents used in therapy of cardiogenic shock should be administered, including fluids and pressors, because the patient may have myocardial damage from heat injury per se or lactic acidosis. This is not only the recommended treatment here at Parkland but it is also advocated by many others.[6-8]

Second, I would like to address his comment on the method of lowering the core temperature in heat stroke patients. In the article from *The Lancet* that was referred to, comparison was made between immersion in an ice bath and having the patient lie on a net suspended over a bath with atomized water at 15°C being sprayed continually from above and below while air at various temperatures was blown over the subject to evaporate the wet surface.[2] The beginning core temperature of the volunteers was 39.5°C before they underwent the experiment. However, it is generally recommended that the active cooling process of heat stroke patients be curtailed when core temperature reaches 39°C.[3,8,9] Indeed, the commonly employed definition of heat stroke includes, among other things, hyperpyrexia to a temperature of greater than 41°C.[3,6,8] Comparison between the various cooling procedures down to a core temperature of 39°C mentioned by the authors of *The Lancet* article showed no significant difference in the time it took to cool the volunteers between any of the methods of lowering body temperature. I know of no study in the literature comparing the differences in morbidity and mortality between the various methods used to cool core temperature in heat stroke patients. I suspect the outcome for victims of heat stroke is determined more by attention to an airway, avoiding aspiration, searching for infection, treating central nervous system abnormalities including coma and convulsions, and watching for cardiovascular complications and arrhythmias, than the method chosen for cooling the patient.

Third, the medical residents who staff the emergency room at Parkland are well instructed in all the various modalities of lowering body

temperature including advantages, disadvantages and hazards associated with each method. The decision as to which one to employ is left to the resident in charge who in turn uses his or her clinical judgment, depending on the circumstances involved and the particular aspects of each individual case, to decide what is best for the patient.

Finally, the comment was made by Dr. Farrell that the patient who was shown on the CBS Evening News being given the ice treatment died the following day, implying that the method chosen for lowering the body temperature was somehow responsible for hastening this patient's demise. Without going into the details of the case, I must emphasize that this particular patient died from something completely unrelated to her heat illness.

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Correction: Hypoglycemia and Accidental Hypothermia

To the Editor: Due to typing errors in the preparation of my manuscript, "Hypoglycemia and Accidental Hypothermia in an Alcoholic Population" (West J Med 133:105-107, Aug 1980), some inconsistencies are present in the article as published. I wish to correct them.

First, on page 106, under the heading "Patients and Methods," paragraph 2, the second sentence should read as follows: "The highest serum glucose value was *317* mg per dl in a patient with chronic pancreatitis (case 2)." The manuscript stated (incorrectly) "*314* mg per dl" and this figure is not consistent with the data given in Table 1.

Second, the survival statistics quoted in the text are inconsistent with the data in Table 1. Case 10 is listed as "Alive" in the table; that patient, in fact, died. The text is correct.

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Asymmetrical Hearing Loss

To the Editor: In the August 1980 issue, Dr. Joseph LaDou reviews the subject of asymmetrical hearing loss in noise-exposed industrial populations.[1] His conclusion, based on a study by Alberti and co-workers,[2] is that "in [cases of] unexplained asymmetrical thresholds, otologic and audiologic consultations should be obtained, as well as vestibular tests, x-ray studies of the temporal bone and advanced hearing tests as indicated." I agree with Dr. LaDou, but feel that his discussion of the data may be misleading and seems to justify an opposite conclusion.

In the study he refers to, 281 patients were evaluated otologically because of pure-tone threshold asymmetries exceeding 15 dB, averaged at 0.5, 1, 2 and 4 kHz. Of these, 108 had extensive workups for retrocochlear disorders, usually including vestibular testing and tomography. Dr. LaDou states that "no treatable disorders were found." In fact, the point of the study was that no treatable *retrocochlear* disorders were found (one arachnoid cyst was discovered). Almost a third of the study group (92/281) had medically or surgically treatable disorders: otosclerosis, otitis media, otitis externa and Meniere disease. Another 54 patients received specific diagnoses other than noise-induced hearing loss or idiopathic sensorineural hearing loss; these included congenital hearing loss, Paget disease, sudden hearing loss and posttraumatic cases. Overall, in more than half the group there were specific diagnoses. Even when medical or surgical treatment is not possible, this information is useful for prognosis, counseling and (obviously) compensation purposes. Presumably, aural rehabilitation and hearing aids were also recommended for many of these patients.

The incidence of specific and treatable diagnoses may be even higher in workers whose asymmetrical hearing thresholds are discovered on routine audiometry as part of an industrial hearing conservation program. Alberti's patients were seen for assessment of compensation, after a noise-exposed career, with an average age of 60.[2]

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The entire Medicaid mess can be blamed on the total lack of foresight by some planners in this country. The high ideals of the late 1960's were translated into the Medicaid program which was going to provide mainstream care for all Americans. After a trial period of some 15 or so years the experiment has proved a dismal failure. The two-class system of care is now more entrenched than it ever was and the costs have been staggering. At the time Medicaid was introduced, there were a number of county hospitals in the state of California providing very good care for those less fortunate or more unwilling citizens (less fortunate because of their illness or because of financial impecunity; more unwilling because a small segment of the population could never be motivated to work). The rolls for California's Medicaid program (Medi-Cal) have skyrocketed to the point that more than 16 percent of California's population is covered by that program. The financing has been inadequate and the restrictions have been burdensome for the physicians taking care of these patients. It is no surprise therefore that most of the physicians of the state are reluctant to see new Medi-Cal patients.

Perhaps more devastating has been the impact of the Medi-Cal program on those hospitals that formerly took care of indigent patients. Several of them have disappeared into the night. Many of them have lost their affiliations with the universities, which provided excellent ongoing care by young physicians and specialists in training, well supervised by the established practitioners in the

a full ten-day stay. The physicians, too, are changing, and moonlighting physicians are commonplace in county hospital facilities.

It is my belief that having embarked on the road of destroying the county hospitals the government should complete the job. With the savings that would be gained, the local administrations and the state could provide realistic remuneration for the hospitals and the physicians in the private sector to take care of these patients.

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Psoriasis and Diet

To the Editor: I enjoyed very much the excellent discussion in September's Medical Staff Conference, "Psoriasis." The conclusion of the discussion that we now have no ideal treatment for psoriasis is clearly valid. Still, I would like to mention a personal experience that has left me wondering just what causes psoriasis and if proceeding with a different kind of research would be useful.

In 1968 my wife, a registered nurse, developed a rash that gradually progressed to a moderately severe psoriasis. Although we sought the finest dermatological treatment, the rash persisted: she held it in check with topical steroids. After seven years of this she discovered by using an elimination diet that the rash resolved when she stopped eating fruits (especially citrus fruits), nuts, corn and milk.

Although this is only one case, it was carefully studied, so I felt reasonably comfortable in trying a similar program on five of my patients. All improved. I also asked them to stop using such acidic foods as coffee, tomatoes, sodas and pineapples because empirically I had found this helped. In fact, elimination of acids has helped a number of patients with various rashes during the five years I have used it. This method is without side effects, simple, easily administered and reasonably effective. Although not ideal, it may be worth considering for certain cases.

Theoretically, this approach makes some sense because our gut bacteria, fungi and viruses make substances that we sometimes absorb (B_{12} for one),[1] and these flora must eat what we put in our intestines. Their excretions are probably directly related to the substances they ingest. Perhaps some gut-flora excretions cause drug-type eruptions because gut-microorganisms synthesize drug-like substances when we ingest certain items.

We might benefit by addressing more research to the chemical reactions (gut secretions plus ingested substances) and gut-flora eliminations that take place when people eat certain cooked[2] and uncooked[3-5] foods and combinations of them.

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Repository, Not Respiratory

An error has been noted in a letter, "Triamcinolone and Keloids," by Ernst Epstein, MD, in the September issue, page 257. In typsetting, the word *respiratory* was twice substituted for *repository*. The section affected should have read as follows: "However, there are three, not two, commercially available *repository* triamcinolone injection materials. Triamcinolone hexacetonide was not mentioned. This salt is the least soluble, and therefore the longest acting of the *repository* triamcinolone preparations on the market" [italics added].

—ED.

Refer to: Davidson TM, Calloway CA: Tonsillectomy and adenoidectomy—Its indications and its problems (Information). West J Med 133:451-454, Nov 1980

Information

Tonsillectomy and Adenoidectomy

Its Indications and Its Problems

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San Diego

APPROXIMATELY 750,000 AMERICANS undergo tonsilleetomy and adenoideetomy (T&A) eaeh year, incurring a eost approaehing one billion dollars annually. The first eombined T&A proceduree was reeorded in 3000 BC and yet with five thousand years' experience there is still strong controversy regarding the risks and benefits of one of the most common surgieal proeedures earried out. The indications for adenoideetomy, tonsilleetomy, or the two eombined, vary from life-threatening illnesses to problems of only minor disability.[1] Similarly, the risks vary from minor to major. In an effort to plaee these variables in proper perspective, the eurrent indieations for and complieations in earrying out a tonsillectomy, adenoidectomy or eombined T&A will be discussed.

Surgical Indications

It must first be understood that there are no absolute cireumstanees for any surgical proceduree, but there are very strong indications. For a tonsilleetomy they are as follows: (1) Carcinoma of the tonsil can oecur in any age group. Lymphoma ean be found in the tonsil in young and older adults and epidermoid careinoma of the tonsil is seen in patients with long smoking and drinking histories. Biopsy is necessary for diagnosis and the best teehnique for biopsy, staging and control of bleeding requires complete removal of that tonsil. Contralateral tonsilleetomy is not necessary. (2) Peritonsillar abseess is eaused by a bacterial infeetion, most often anaerobic in nature. Ineision and drainage is mandatory to prevent extension of the infeetion into the spaee about the earotid artery. Ineision and drainage, and appropriate antibiotic therapy is eurative for an aeute episode. About 8 pereent to 10 pereent of peritonsillar abseesses reeur, and beeause of the destruction of the peritonsillar spaee by the first abseess, a reeurring abscess often extends rapidly into the parapharyngeal spaee and may be quickly fatal. Therefore, it is eonsidered wise to carry out a tonsilleetomy for peritonsillar abseess. This may be done either at the time of the initial discovery of the abseess or electively six weeks later. This is a decision which should be made by the patient and surgeon together aecording to their own needs and philosophies. (3) Congestive heart failure is sometimes seen in young ehildren. This can be eaused by a persistent upper airway obstruetion, and presents as a fairly elassic ease of right-sided heart failure. The airway obstruetion is most eommonly eaused by the tonsils. Tonsilleetomy, usually in association with adenoidectomy will alleviate the airway obstruction and reverse the entire cardiae process.[2] (4) Aeute tonsillitis is sometimes so severe that respiratory difficulties and significant dysphagia develop, requiring the patient to be admitted to hospital. It is our feeling that any episode of tonsillitis eausing respiratory embarrassment or dysphagia so severe that hospitalization is required is best treated by elective tonsilleetomy six weeks after resolution of the tonsillar infeetion.

The two most eommon "philosophieal" indieations for tonsilleetomy involve deeisions whieh must be made both by patient and physician. The first, recurrent tonsillitis, is a very elusive disease.[3] Many patients have a history of multiple episodes of recurrent tonsillitis, usually in abundance of 6 to 12 per year. However, this is diffieult to doeument. Very often if these patients are followed closely, they may have far fewer episodes per year. In addition, evidence of a beta-hemolytie streptococcal tonsillitis as opposed to a viral upper respiratory tract infeetion is diffieult to doeument. The entire picture is eonfused by the inaccuracies of the eommon throat eulture for beta-hemolytie streptocoeei. Nonetheless, it is currently felt by most otolaryngologists that a patient having four or more episodes of baeterial tonsillitis a year for at least two years, necessitat-

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From a paper presented at California Medical Association's 109th Annual Session in San Diego, February 10, 1980.

Reprint requests to: Terence M. Davidson, MD, Department of Surgery/Otolaryngology, University Hospital, 225 West Dickinson St., San Diego, CA 92103.

TABLE 1.—*Current Indications for Tonsillectomies and Adenoidectomies*

Tonsillectomy—Strong Indications

- Carcinoma of the tonsil. The best technique for optimal results from biopsy and staging requires complete removal of the tonsil.
- Peritonsillar abscess (PTA). PTA is a bacterial abscess, most often anaerobic. Incision and drainage is mandatory. Recurrent abscess rate is 8 percent to 10 percent and recurrent abscess may be fatal. Therefore, the tonsil should be removed. This may be done at the time of the initial PTA presentation or may be done electively six weeks later.
- Congestive heart failure. Right-sided heart failure can be caused in young children by a consistent upper airway obstruction. This is reversed by tonsillectomy.
- Tonsillitis causing respiratory difficulties, dysphagia and requiring hospitalization. Any episode of tonsillitis causing respiratory embarrassment, or so severe that hospitalization is required, is best treated by elective tonsillectomy six weeks after the episode.

Tonsillectomy—Philosophical Indications

- Recurrent tonsillitis. It is currently felt by most otolaryngologists that a patient having four or more episodes of tonsillitis a year for at least two years and necessitating their missing ten or more days a year of school or work will benefit from a tonsillectomy.
- Recurrent otitis media. In some patients acute otitis media always or frequently develops following upper respiratory tract infections. If these cannot be successfully treated prophylactically with antibiotics, beginning at the onset of the upper respiratory tract infection, it may be an indication for tonsillectomy and adenoidectomy.

Adenoidectomy—Strong Indications

- Nasal airway obstruction. This is often associated with hyponasal speech and tongue thrust with maxillary dental protrusion. Very few cases warrant adenoidectomy for the latter reasons alone, but the few that do will benefit.

Adenoidectomy—Philosophical Indications

- Recurrent tonsillitis. A prepubertal patient with recurrent streptococcal tonsillitis who is to be treated by tonsillectomy should have adenoidectomy at the same time.
- Serous otitis media. Some cases of serous otitis media, recurrent and/or persistent, may be "cured" by adenoidectomy. To date, no one knows how to select those who will benefit from this operation. Therefore, patients with prolonged serous otitis media associated with a conductive hearing loss and/or retraction of the tympanic membrane should have myringotomy with insertion of middle ear ventilation tubes. If they have large adenoids, documented by a soft tissue lateral x-ray study or nasal obstruction, adenoidectomy may be of significant benefit. If the patient has large tonsils and recurrent tonsillitis particularly predisposing to ear infections, tonsillectomy should be carried out as well.

TABLE 2.—*Morbidity and Mortality in 6,175,729 Tonsillectomies and Adenoidectomies**

Condition	*Percent*
Mortality	
Anesthesia	0.002
Cardiac arrest	0.002
Hemorrhage	0.002
TOTAL	0.006
Hemorrhage	
Requiring carotid ligation	
• Immediate postoperative period	0.008
• Delayed postoperative period	0.02
Requiring 5 or more units of blood	0.009

*According to Pratt.[6]

ing their missing ten or more days a year of school or work, will benefit by tonsillectomy. This is of course a philosophical decision—one which the patient must ultimately make after he or she understands the risks and potential benefits of that procedure. Many physicians feel that recurrent otitis media is the other most common indication for tonsillectomy. While this is not always so, in some patients an upper respiratory tract infection occurs which develops into serous otitis media and finally acute otitis media. If these progressive conditions cannot be successfully treated prophylactically with antibiotics, then tonsillectomy and adenoidectomy may be warranted to try to prevent acute otitis media from recurring. One might be particularly swayed in this direction if acute otitis media always resolves into a long bout of serous otitis media associated with a conductive hearing loss.

Adenoidectomy is strongly indicated in young patients with severe obstruction of nasal airways. This can often be associated with hyponasal speech and tongue thrust with maxillary dental protrusion.[4] Although there are very few cases which warrant adenoidectomy for these latter reasons alone, the few that do can benefit greatly.

Thus, most indications for adenoidectomy are philosophical. In prepubertal patients with recurrent streptococcal tonsillitis who are to be treated by tonsillectomy, adenoidectomy should usually be done at the same time. Encircling the oronasopharyngeal areas is a ring of lymphoid tissue known as Waldeyer ring. The tonsils and the adenoids are the major lymphoid tissues of this ring. Most commonly, streptococcal tonsillitis involves the adenoids, and it is best to do an adenoidectomy concurrently with the tonsillectomy. In patients with cleft palates and even in those

with submucous cleft palates in whom nasopharyngeal incompetence is at risk, adenoidectomy should be avoided; it is wise to avoid tonsillectomy as well.

Serous otitis media is a disease which affects as many as 20 percent of school-age children. Its cause remains elusive and is most likely multifactorial. Very clearly, in some patients serous otitis media develops because of adenoidal obstruction of the eustachian tube into the nasopharynx. These patients presumably will benefit by removal of the adenoids. No one knows what percentage of patients with prolonged serous otitis media associated with conductive hearing loss or retraction of the tympanic membrane have their eustachian tubes obstructed by adenoidal tissue. Therefore, cases of patients with severe otitis media and large adenoids should be considered for adenoidectomy—carried out ordinarily at the time of myringotomy—and insertion of ventilation tubes. Large adenoids can be documented by a soft-tissue lateral x-ray study, and are strongly suggested by nasal obstruction as well. However, once again, this is a philosophical decision, which must be decided on mutually by the treating physician and the patient's parents. Similarly, if the patient has large tonsils, these may compress the inferior aspect of the eustachian tube, and tonsillectomy should be considered, particularly if the patient has a history of recurrent tonsillitis, and if the recurrent tonsillitis predisposes to ear infection.

Morbidity and Mortality

The indications for tonsillectomy and adenoidectomy are summarized in Table 1. Before one can recommend an operation, one must understand the risks that are incurred by such a procedure. The risks of morbidity and mortality from T&A range from postoperative throat discomfort to death.[5] In one of the largest studies of T&A, consisting of 6,175,729 cases, Pratt[6] showed a mortality of one per 16,381 (0.006 percent) (see Table 2). This study showed that anesthesia was responsible for 139 deaths, or one per 44,429 (0.002 percent). Cardiac arrest occurred in 27 patients, or one per 48,627 (0.002 percent). Hemorrhage occurred in 111 patients, or one per 55,637 (0.002 percent). In this same study, hemorrhage was examined as a severe cause of morbidity. Catastrophic bleeding requiring carotid artery ligation occurred during the immediate postoperative period in 504 patients, that is, one per 12,253 (0.008 percent), and in the delayed postoperative period, 1,496 patients, or one per 4,128 (0.02 percent). Bleeding requiring transfusions of more than 5 units occurred in 538 patients, or one per 11,479 (0.009 percent). In 1965 Alexander[7] found the mortality to be 1.03 per 10,000 tonsillectomies, with most deaths related to the following factors: (1) lack of observation, (2) usage of ether anesthesia rather than halothane, (3) higher mortality in patients more than 15 years old and (4) lack of decisiveness by the surgeon confronted with hemorrhage. There was an absence of mortality in patients in whom tonsillectomies were done under local anesthesia. In a study done by Tolczynski,[8] he quoted the Commission for Professional Hospital Activities as finding that postoperative hemorrhage had the following incidence: ear, nose and throat specialists, 1.9 percent; general surgeons, 2.5 percent; and general practitioners, 3.4 percent. Every 13th physician in the study lost at least one patient because of bleeding following T&A.

Other complications of T&A procedures are multiple and include the following: the incidence of nasopharyngeal stenosis is approximately three in 100,000 T&A's.[9,10] A variety of less common complications have been reported and these include: acute cervical adenitis, occasionally with abscess formation and suppuration,[11] extending to deep compartments of the neck; airway obstruction secondary to subglottic edema resulting from intubation; aspiration of foreign bodies, particularly blood clots; mediastinal emphysema; rupture of pulmonary blebs and alveoli; otalgia; palatal incompetence; and food, fluids and air escaping from the nose. Rhinolalia aperta (air escapage from the nose) is relatively common. However, it is very uncommon for food, fluid or air escapage from the nose to be a long-term sequella. Dental dislocation secondary to mouth gags and intubation occurs most frequently in children with deciduous teeth. Uvular edema often seen with cautery is common, but is rarely of significance. Uvular amputation can also occur but is of no significance.

A variety of diseases have been reported in association with tonsillectomy, and these include Hodgkin disease,[12] multiple sclerosis[13] and poliomyelitis.[14] None of the studies are definitive, although some of them seem conclusive; nevertheless, in almost all cases there are additional studies equally well done which have opposite conclusions. In all of these cases it is difficult to screen

out those patients in whom a disease (such as Hodgkin disease or appendicitis) would have developed despite T&A being done. The indications used as the basis for carrying out T&A may represent the early manifestations of those diseases. While it may be possible that the tonsils play an important role in protection against Hodgkin disease, no one has ever provided strong evidence that this is true.[15]

The major causes of morbidity and mortality associated with these operations are as follows: All patients undergo the usual fears of surgical procedures and almost all patients undergo a certain amount of postoperative discomfort. Postoperative bleeding may be as common as one case per 100, but it is very seldom serious. Although it may be terrifying, it should result in death only very rarely. Death from anesthesia also occurs. These causes combined result in a mortality of approximately one patient in 16,000 (0.006 percent).

Conclusions

The number of tonsillectomies and adenoidectomies carried out each year has been significantly reduced. Yet too many are still done without proper indications. Some patients who stand to benefit significantly from these procedures are denied the opportunity by physicians who are afraid of the risks posed by the operation or are unconvinced of its beneficial effects. There is no dogma for these diseases. Many surgeons associated with skilled anesthesiologists have very few complications, and for these, indications can be broader. The converse is also true. Patients have fears, feelings and philosophies. These, too, must be considered. Some patients need to be swayed toward an operation and others must be dissuaded. This is the skill and the art of medicine.

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Information

The Neuropathies of Leprosy

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LEPROSY IS THE most common treatable neuropathy in the world,[1] yet many physicians in nonendemic areas are unfamiliar with this disease. While it is an uncommon cause of neuropathy in the United States, the following cases show the need to consider leprosy in the differential diagnosis of both symmetrical polyneuropathy and mononeuritis multiplex, especially in regions where substantial foreign migration occurs. These cases will also help to illustrate the broad clinical spectrum of leprosy from lepromatous to tuberculoid forms.

Reports of Cases

CASE 1. A 30-year-old Mexican-American man was referred with a two-year history of loss of sensation in the hands. He had noted diminished sensation of pain and temperature in both arms, followed by a more recent loss of sensation in the

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feet. This deficit resulted in painless trauma to his extremities and occasional cigarette burns on his fingertips. In addition, the patient noted a "heavy feeling" in his arms and legs and some weakness of his grip. Evaluations at two other university centers had resulted in a diagnosis of idiopathic polyneuropathy. The patient consumed a moderate amount of alcohol and smoked one pack of cigarettes a day.

A physical examination showed foreshortened, deformed fingers with crusted ulcers (Figure 1A) as well as deep penetrating ulcers over the soles of the feet (Figure 1B). Ulnar and peroneal nerves were enlarged to palpation. Fasciculations were present in the forearm muscles, and there was mild wasting and weakness of distal muscles in the upper and lower extremities. There was a dissociated sensory loss with severe impairment of pain and temperature sensation below the knees and elbows with only a mild distal loss of position and vibration senses. The Romberg test was positive.

Laboratory abnormalities included a leukocytosis of 13,900 per cu mm and a mild elevation of alkaline phosphatase, lactate dehydrogenase and serum aspartate aminotransferase (formerly called serum glutamic oxaloacetic transaminase, SGOT) levels.

Findings of electrophysiological studies were consistent with a generalized polyneuropathy. Distal muscle sampling with a needle electrode disclosed chronic partial denervation, while proximal muscle testing gave normal results.

Sensory nerve action potentials were not detectable over the median, ulnar or sural nerves. Motor nerve conduction velocities could not be measured in the peroneal or posterior tibial nerves because no muscle response could be elicited in the extensor digitorum brevis or abductor hallucis longus, respectively. The right median motor nerve conduction velocity, between elbow and wrist, was 38 meters per second (normal greater than 51 meters per second), with a distal motor latency of 4.5 msec (normal less than 4.7 msec). In the right ulnar nerve, from above elbow to wrist, the motor nerve conduction velocity was 35 meters per second (normal greater than 49 meters per second), distal motor latency 4.5 msec (normal less than 3.5 msec), and compound muscle action potential amplitude 2 mV (normal greater than 4 mV).

A biopsy specimen obtained from an area of alopecia on the left forearm showed chronic, minimal mononuclear cell infiltration in a perivascular distribution. Fite stain showed numerous acid-fast organisms.

The sural nerve biopsy specimen showed marked demyelination with some sparing of axons, as well as a severe inflammatory infiltration with plasma cells and lymphocytes. Acid-fast organisms resembling *Mycobacterium leprae* were scattered abundantly throughout the tissue. Granulomas and giant cells were absent. The histological features were compatible with those of lepromatous leprosy (Figure 2).

A lepromin skin test was nonreactive. Treatment with dapsone (4.4′-sulfonyldianiline) was begun and the patient was referred to the Public Health Service Hospital in Carville, Louisiana.

CASE 2. A 22-year-old Vietnamese man complained of weakness and numbness in his right arm. Beginning in 1971 he had noted paresthesia

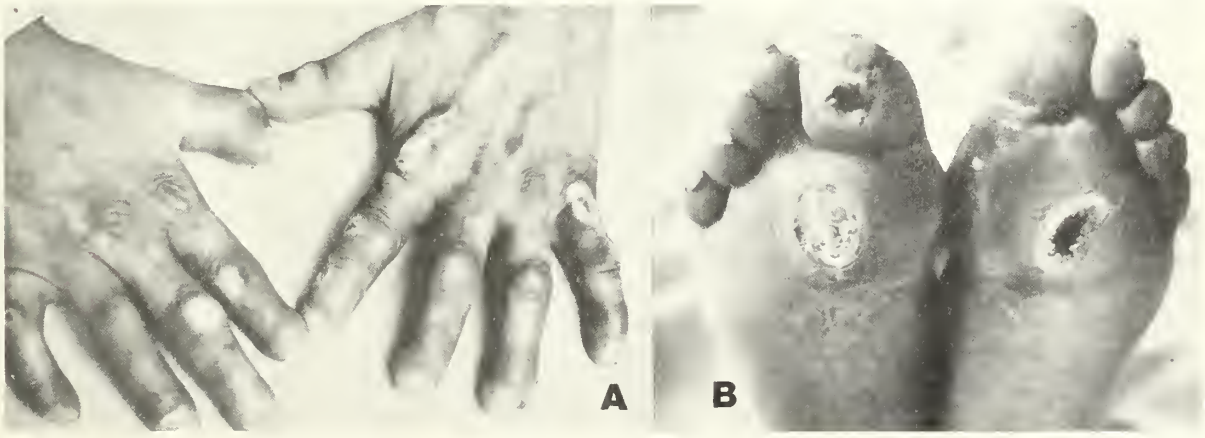

Figure 1.—A, Hands of patient (case 1) showing the characteristic trophic changes of leprosy: distal absorption, atrophy and ulceration. **B,** Prominent ulceration of the same patient's feet.

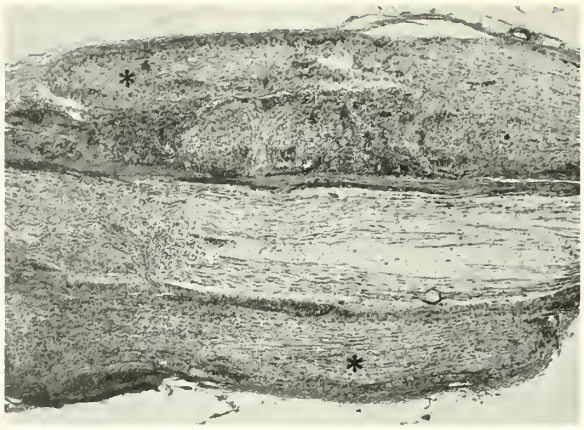

Figure 2.—Sural nerve tissue specimen from patient (case 1). The transverse section shows a central nerve bundle containing a decreased number of myelinated nerve fibers as well as scattered mononuclear cells. The perineurium (*) is thickened and contains a massive infiltration of small mononuclear cells. Granulomas and giant cells are absent. (Hematoxylin-eosin stain; magnification ×40 before reproduction.)

in the right arm as well as a gradually diminished sensation of pain. He first noted weakness in the right hand in 1973, and this gradually progressed to almost complete paralysis by January 1977.

The diagnosis of leprosy was made in 1977, while the patient was in Malaysia. A regimen of dapsone was begun, which the patient discontinued after 1½ months. He was first seen in the dermatology clinic at our institution in July 1978. A biopsy specimen was obtained from a questionable skin lesion over the right elbow, but showed no evidence of leprosy.

Apart from several small posterior cervical lymph nodes and an enlarged right epitrochlear node, the general physical examination including integument was unremarkable.

Forearm muscles and intrinsic muscles of the right hand were substantially atrophic with flexion contractures and shortening of the fingers. Muscle strength was graded as 4 (Medical Research Council Scale, 0 to 5) in the right biceps, triceps, wrist extensors and flexors, and 3 in the intrinsic muscles of the right hand. Greater auricular, ulnar and peroneal nerves were palpably enlarged bilaterally. A dissociated sensory loss was found, with profound loss of pain and temperature perception in the right arm distal to the midhumerus; there was only a moderate loss of vibration and light touch in the same area. Perception of light touch, pain and temperature were mildly diminished in the right leg below the knee. Results of routine laboratory tests including a complete blood count, multichemistry screen, coagulation studies, analysis of urine, electrocardiogram and x-ray study of the chest were normal.

Electrophysiological studies documented mononeuritis multiplex involving the right ulnar, median, radial and sural nerves. Nerve conduction velocities and sensory action potentials were unobtainable in the right median, ulnar and radial nerves. The right sural sensory action potential was also unobtainable. Motor and sensory conduction studies gave normal results for the left ulnar, left median, right peroneal and left sural nerves.

Muscle sampling with a needle electrode gave normal results in the right biceps, triceps and brachioradialis. There was complete denervation in the extensor indicis proprius (radial nerve), first dorsal interosseous (ulnar nerve) and the abductor hallucis brevis (median nerve) muscles.

A biopsy specimen of the right sural nerve showed complete replacement of the nerve by intense granulomatous inflammatory reaction. A small number of acid-fast organisms were found limited to focal areas of nerve. These findings are compatible with tuberculoid leprosy. Because his sister was believed to have dapsone-resistant leprosy, the patient was treated with 50 mg of dapsone twice a day and 100 mg of clofazimine each day.

Case 3. A 51-year-old Vietnamese man was admitted for evaluation of gradually progressive weakness and numbness of the right lower extremity of a year's duration. He had lost 6.75 kg (15 pounds) over the year preceding admission. Past medical history was unremarkable and the patient was not taking medication.

There was wasting and complete paralysis of the right tibialis anticus, extensor digitorum brevis, extensor hallucis and peronei. Decreased pin and light touch perception were noted in the right peroneal nerve distribution.

Results of laboratory studies including a multichemistry screen, a test for antinuclear antibodies and examination of cerebrospinal fluid were normal. The erythrocyte sedimentation rate was slightly elevated at 29 mm per hour. There was an increased gamma globulin fraction, measuring 2.24 grams per dl (normal, 0.6 to 1.4) on serum protein electrophoresis. Tuberculin skin test (purified protein derivative [PPD]) was reactive, 2 by 2 cm.

Lumbar spine films showed a vertebral com-

pression fracture at L-4. Findings of a lumbosacral myelogram were within normal limits.

Electrophysiological studies documented a right-sided common peroneal neuropathy. The motor conduction velocity for the right peroneal nerve could not be determined because no response could be obtained in extensor digitorum brevis or tibialis anterior. The motor nerve conduction velocity, distal motor latency and compound muscle action potential amplitude over abductor hallucis longus were all normal for the right posterior tibial nerve. Sensory nerve action potential over the left sural and the right and left median nerves was normal. Muscle sampling with a needle electrode gave normal results in right semitendinosis, biceps femoris and gastrocnemius. There was complete denervation in the tibialis anticus and peroneus longus.

Results of two punch biopsies of skin were unremarkable. Histological findings on the right sural nerve biopsy specimen were compatible with tuberculoid leprosy. There was extensive demyelination and loss of axons with collagenous replacement of nerve. Pronounced perineural thickening was accompanied by a chronic inflammatory response, including multinucleated giant cells and small granulomas. No organisms were seen on acid-fast stain.

Dapsone therapy was begun and the patient was fitted with a leg brace.

Comment

Clinically and histologically, peripheral neuropathies in leprosy may be divided into two main types, lepromatous and tuberculoid.

Lepromatous leprosy (Table 1) is associated with a defective immune response and negative results on a lepromin skin test. There is commonly a symmetric polyneuropathy with sensory loss simulating a stocking-glove pattern. However, careful analysis of the sensory loss shows that it begins in the coolest parts of the body, such as the pinna of the ears, dorsal surface of the hands and feet, dorsoradial forearm and anterolateral aspect of the lower legs.[1] Mononeuritis multiplex superimposed on a symmetrical polyneuropathy has also been described in lepromatous leprosy.[2] Sensory loss in lepromatous polyneuropathy is due to intracutaneous infiltration of organisms and the corresponding inflammatory response. Hematogenous spread of bacilli may result in involvement of several organs. Acid-fast organisms may appear in large numbers in the endoneurium and perineurium and within Schwann cells. Eventually, endoneurial elements are replaced by collagen, and granulomas are rarely observed. Polyneuropathy, negative lepromin skin test and biopsy findings in case 1 are consistent with lepromatous leprosy.

Tuberculoid leprosy (Table 1) is associated with a relatively intact immune response, including a positive lepromin skin test. Characteristically, there are hypopigmented macules or papules that are frequently anesthetic, though these were not seen in the cases discussed above. The cutaneous and subcutaneous nerves are those most frequently affected and may be clinically enlarged. The histological features include formation of granulomas with epithelioid cells as well as Langhans and foreign body giant cells. Extensive axonal loss occurs with perineurial and endoneurial thickening. Bacilli are rare or absent. The neuropathy can be more extensive if nerve trunks are invaded; for example, in case 2 there was right median, ulnar and radial polyneuropathy and in case 3 a right-sided common peroneal mononeuropathy.

In dimorphous or intermediate leprosy clinical and pathological characteristics of both lepromatous and tuberculoid leprosy may be present. A small percentage of patients with the disease manifest only solitary hypopigmented macules which may be analgesic (indeterminate form). Peripheral nerves are always involved in leprosy,

TABLE 1.—*Major Features Distinguishing Lepromatous and Tuberculoid Leprosy*

Feature	*Lepromatous*	*Tuberculoid*
Immune response	Impaired	Relatively intact
Lepromin skin test	Negative	Positive
Neuropathy	Intracutaneous; mimics stocking-glove pattern	Anesthetic macules; mononeuritis multiplex
Skin lesions	Multiple, variable	Few, hypopigmented
Hematogenous spread	Positive	Negative
Pathology	Diffuse inflammation; no granulomas; many acid-fast bacilli	Granulomas; few acid-fast bacilli

TABLE 2.—*Diagnosis of Leprosy*

Sensory loss
Precedes weakness
Dissociation (pin and temperature>position and vibration)
Intracutaneous pattern
Motor involvement
ulnar=peroneal>median
Preserved tendon reflexes
Enlarged nerves
Trophic changes
Absorption of digits
Positive findings on nerve or skin biopsy studies

although frequently this feature is not clinically evident. Conversely, neuropathy without the cutaneous manifestations of leprosy (that is, primary polyneuritic leprosy) is common in some series.[3]

Results of electromyography and nerve conduction studies in leprosy are nonspecific and merely reflect the sensory-motor components of the accompanying neuropathy.[4,5] The findings of chronic denervation, impaired sensory conduction and abnormal motor nerve conduction velocity in these patients are consistent with previously reported electrophysiological abnormalities in leprosy.[2,4,5] Such electrophysiological abnormalities have sometimes improved following appropriate chemotherapy.[2] Subclinical involvement of the sural nerve may be detected by nerve conduction studies, thus providing a readily accessible biopsy site (case 2).

Several clues may be helpful in making the diagnosis of leprosy (Table 2). Sensory loss reliably precedes weakness. As seen in cases 1 and 2, there may be a dissociation of pin and temperature sensations from other sensory modalities, which reflects a preferential loss of small sensory fibers. Careful testing may indicate the intracutaneous pattern of sensory loss with the coolest body parts involved first. Weakness in lepromatous leprosy generally appears first in the distribution of the ulnar and peroneal nerves followed by the median nerve. Deep tendon reflexes are usually maintained, even with a severe neuropathy. Nerve enlargement, trophic ulceration and absorption of fingers are often present. Findings on skin or nerve biopsy studies may be diagnostic and useful in differentiating leprosy from diseases that may have a similar clinical presentation, such as lymphomatoid granulomatosis.[6]

Two of the three patients discussed in this paper are of Vietnamese extraction and are part of the recent influx of some 4,000 Vietnamese into the Portland area. These cases serve to point out the clinical variability of neurological involvement in leprosy, and to emphasize the need to consider leprosy as part of the differential diagnosis of neuropathy in patients who emigrate from areas where it is endemic.

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CONTINUING LEARNING IN THE PROFESSIONS—Cyril O. Houle, Senior Program Consultant, W. K. Kellogg Foundation; and Professor Emeritus of Education, University of Chicago. Jossey-Bass Publishers, 433 California Street, San Francisco (94104), and Jossey-Bass Limited, 28 Banner St., London ECY 8QE, 1980. 390 pages, $15.95.

Members of the medical profession will find Professor Cyril Houle's book *Continuing Learning in the Professions* interesting, illuminating and useful. For those who plan and produce continuing education activities, the book is essential.

The author, considered the dean of continuing education in the United States, has produced a book that will rapidly become the standard reference in the field.

Based on a study of 17 professions and a lifetime experience, the book begins with a discussion of the societal pressures facing all professions and points out that although "no single course of action can resolve the difficulties . . . ," lifelong learning is necessary for all professionals to maintain and improve their service to society. Houle presents a careful study of the key ideas that will help professionals plan their continuing education. Three major modes of learning are described: inquiry (development of new ideas, techniques or policy); instruction (dissemination of information) and performance (learning to practice an idea habitually).

Professor Houle proposes that the present goals of continuing education be broadened to be compatible with the overall characteristics and functions of professions. Improving mastery of theoretical knowledge, problem-solving, practical application of knowledge, and self-enhancement are also considered. Professor Houle further suggests that professions establish standards for formal training and awarding of credentials, and encourage legal reinforcement, public acceptance and interrelations with other vocations.

In the chapter "Lifespan Learning of the Professional" Professor Houle states that in a ten-year search he has been unable to identify an admission committee that tried to estimate the continuing education potential of its applicants.

Chapter 5 emphasizes the importance and mechanics of a "zest for learning," and there are excellent chapters on "Providers of Continuing Professional Education" and "Designing Programs of Learning and Evaluations."

The chapter "Assuring Quality through Continuing Education" will be of particular interest to educators, practitioners and legislators. "As always," Houle writes, "the effort to achieve excellence must be based on the realization that it is ultimately subjective. Procedures can be refined, outcomes can be measured, authorities can be cited, precedents can be followed and data can be brought to bear upon decision-making processes, but qualitative conclusions must always be judgmental. To hope that if some specific procedure is followed the right answer will always be produced is to rely upon dogma. In any situation, past experience may have shown that one way of doing things is generally best, but in particular cases, unknown factors may exist. This is one of the most important lessons a professional, who must always be practical and pragmatic, should learn."

Houle predicts that

"The expansion of continuing education is certain to be sustained. There are slight evidences that the present antagonism against the professions may already have passed its peak and be subsiding, partly as a result of the steps taken to counter it. But any relaxation of dedicated efforts to maintain quality will start new waves of criticism. Learning must occur throughout the lifespan and must assume new and more complex forms. The plans to establish basic educational programs for those entering the professions were thought in the first quarter of this century to be visionary, but they have now been realized at levels far beyond those of the original dreams. Continuing education will follow the same pattern of growth; what we hardly dare prophesy today will be seen by later generations as efforts to achieve and manifest necessity."

The final chapter presents a six-point program for action, emphasizing the following principles:

(1) The primary responsibility for learning should rest with the individual.

(2) The goals of professional education, including those of continuing learning, should be concerned with the entire process of professionalization.

(3) Continuing education should be considered a part of a lifelong process of learning.

(4) The patterns and methods of continuing education should be planned and conducted in one or more of the modes of education: inquiry, instruction and performance.

(5) The provision of continuing education should expand so it pervades all aspects of professional life.

(6) Professions should collaborate on the planning and provision of continuing education.

Continuing education of professionals is the most important uncharted frontier in education. Professor Houle has drawn, from his long and distinguished career in adult education, a blueprint that clearly defines the present state of continuing education and suggests future directions and priorities. Physicians, and especially those who are now working in the expanding field of continuing medical education, will find this book exciting reading.

PHIL R. MANNING, MD
Associate Vice President for Health Affairs
University of Southern California
Los Angeles

* * *

CARDIAC ANESTHESIA—Edited by Joel A. Kaplan, MD, Associate Professor, Department of Anesthesiology, Director, Division of Cardiothoracic Anesthesia, Emory University School of Medicine, Atlanta, Georgia—in the series: CLINICAL CARDIOLOGY MONOGRAPHS—Series Consultants: J. Willis Hurst, MD, and Dean T. Mason, MD. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1979. 530 pages, $44.75.

We have needed an up-to-date textbook devoted to cardiac anesthesia for some years. The number of cardiac operations continues to increase, and there are few anesthesiologists or anesthetists who do not look after patients with heart disease undergoing noncardiac procedures.

This book is timely, and its quality assures instant status as the standard work on the subject. It is written by members of the faculty of Emory Universiy, under the editorship of Dr. Joel A. Kaplan. In his foreword, Dr.

J. Willis Hurst says that "This book . . . is what our anesthesiologists do at Emory University Hospital." That is modestly stated. Anyone teaching cardiac anesthesia notices that his time is spent teaching cardiology, the technology of bypass, intensive care and "hemodynamic pharmacology." This book surveys the entire field in some detail. It invites the anesthesiologist to assume his place as the internist consultant to the cardiac surgical team.

There are four sections. Each chapter, written independently, is a freestanding text on its subject. Naturally this leads to repetition, but this can be accepted because it contributes to the impression of lucidity that the book gives. The lessons repeated are certainly worthwhile; "And what I tell you three times is true" (Lewis Carroll, *The Hunting of the Snark).*

The first section, Pharmacology and Monitoring, has chapters on the pharmacology of anesthetic and cardiovascular drugs, electrocardiographic and hemodynamic monitoring. These are excellent reviews. I have three minor comments. We are shown a picture of the programmable calculator used by the author for derivation of indices from hemodynamic measurements. I would rather have the program listing—I know what a calculator looks like. I feel that the example of hemodynamic therapy used as an illustration (pp. 99-100) does not meet Kaplan's usual notable standard of lucidity, and expansion of this section would be desirable. There is also an illustration (p. 108) showing three data points, referenced to a private communication, which shows the effect of variation in arterial carbon dioxide pressure on the coronary blood flow. While I do not oppose the author's point, that gross hypocarbia should be avoided, without further data the illustration just raises questions. Respiratory acidosis cannot be good for the coronary patient, can it?

The second section, Disease Entities and Anesthesia, presents preoperative management. There is then a long chapter on acquired valvular heart disease presented with ventricular pressure/volume loops as the teaching mode. Anesthesia residents found this heavy going, but it teaches wonderfully if read together with the catheterization report the day before a case. Discussion of each valve disease is ended with "anesthetic considerations," undogmatically stated. Also, in this section are presented anesthesia for coronary revascularization and anesthesia for treatment of congenital heart defects. This chapter, almost an independent textbook, could be improved only by the addition of a few simple diagrams of the lesions described and the ingenious operations carried out. The final chapters of this section cover pacemakers, thoracic aneurysms and anesthesia for noncardiac surgical procedures in cardiac patients. If you seek information on constrictive pericarditis, it is to be found in the postoperative section, in proximity to discussion of tamponade.

The third section, Support of the Circulation, deals with cardiopulmonary bypass and balloon pump support, at a level seldom found in anesthesiological works. This makes the book attractive as an introductory text or review for surgeons, perfusionists and others. Five pictures of disposable oxygenators, all mysteriously different, would mean more if there were one diagram of their common functional anatomy. There are checklists to help you prepare to come on and off bypass, and algorithms to suggest what to do next. An illustration (p. 432) of the value of sequential A-V pacing to raise the cardiac output raises my doubt. In order to increase the P-R interval from 0.12 to 0.15 seconds, the heart rate has been increased, and this is more likely to be the reason for the modest rise in cardiac output stated.

The final section, Postoperative Care, starts with a chapter on postoperative intensive care. This is perhaps weaker than the prevailing standard. The section on cardiovascular care includes some would-be algorithms for the treatment of common problems, which suffer because they are not really algorithms, and also not helpful.

The book is almost entirely free of misprints. However, on page 479 the interesting "Isoethrane" is introduced. This is probably "isoetharine." The book is attractively printed and bound, and adequately indexed. At $44.75 it is a heavy investment. The value is there, however. It is needed in the libraries of all teaching programs. It should be welcomed by all practitioners who must look after patients with heart disease. It will be found instructive by members of other disciplines who want a complete background review of the joint endeavors of the cardiac surgical/anesthetic team.

HENRY CASSON, MD
Associate Professor of Anesthesiology
University of Oregon Health Sciences Center
Portland, Oregon

* * *

RECENT ADVANCES IN CLINICAL NEUROLOGY—Number Two— Edited by W. B. Matthews, DM, FRCP, Professor of Clinical Neurology, University of Oxford; and Gilbert H. Glaser, MD, MedScD, Professor of Neurology and Chairman, Department of Neurology, Yale University. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 199 pages, $24.00.

In this relatively short and succinct book, two excellent editors, one from England and one from the United States, have joined forces to select topics that represent some of the more important recent advances in the field of clinical neurology. The editors have chosen a cast of American, English and Australian contributors who are among the top experts in their respective areas of interest. Each author has skillfully summarized the advances that have the most direct application to clinical neurology. The result of their endeavor is an eminently readable, comprehensive, useful and well-referenced update. In the ten chapters, topics such as "The Latest Thoughts on the Etiology and Treatment of Multiple Sclerosis," "Therapy of Acute Ischemic Stroke," "Progressive Dialysis Encephalopathy (Dialysis Dementia)" and "Brain Death" are reviewed. Progress in these areas has been very limited and slow. Consequently very few new ideas have emerged. The chapter "Myasthenia Gravis and Myasthenic Syndromes" reviews the latest concepts of the pathophysiology of these disorders and examines the various therapeutic modes and techniques in a critical manner. The controversy between the proponents of thymectomy by the standard transsternal and the newer transcervical approach is aired yet not resolved.

In the chapters "Clinical Applications of Evoked Potentials" and "The Auditory and Vestibular System," the contributors review and evaluate some of the newer neurophysiological techniques, their limitations and how they can be used by clinicians to elucidate diseases of the optic system (evoked visual responses), the spinal cord and the brain (somatosensory evoked response), and the brain stem (auditory evoked response). The latest classification of pituitary neoplasms, based on electromicroscopic features of the tumor, and updated thoughts on the evaluation of patients and rational treatment are the subject of a very thorough review in another chapter. The chapters dealing with pathophysiology and

treatment of brain edema and raised intracranial pressure with particular reference to normal pressure hydrocephalus are especially useful since they provide practical diagnostic criteria and ideas concerning therapy. The latest in the pathogenesis and treatment of migraine and a workable scheme of aphasia and apraxia are covered in a very succinct and lucid manner. Finally the chapter "Clinical Application of Computerized Axial Tomography (CT Scanning)" attempts to provide a broad outline of certain well-defined, common, neurological problems. However, as the author suggests, the chapter is somewhat superficial and incomplete and is therefore less useful than is the remainder of the book.

Recent Advances in Clinical Neurology—Number 2, is highly recommended. The book should be most useful to students, residents and beginning practitioners of neurology who want a brief but concise update of common neurological problems. The price of the book seems to reflect today's rampant inflation.

PIERRE M. DREYFUS, MD
Professor and Chairman
Department of Neurology
University of California, Davis; and
Chief of Neurology
University of California, Davis,
Medical Center
Davis, California

* * *

CRITICAL CARE MEDICINE MANUAL—Edited by Max Harry Weil, MD, PhD, Chairman and Clinical Professor, Division of Critical Care Medicine and Director of the Institute of Critical Care Medicine, University of Southern California Schools of Medicine and Engineering, Los Angeles; and Protasio L. DaLuz, MD, Hospital das Clinicas da Faculdade de Medicine da Univ. de Sao Paulo, Brazil. Springer-Verlag New York Inc., 44 Hartz Way, Secaucus, NJ (07094), $22.50.

Preliminary inspection of this book generates enthusiastic anticipation. However, in this instance the adage that one cannot tell the contents of a book by its cover proves to be true. The title leads one to believe that this is a reference manual for use in a critical care setting. However, the format does not follow the expected *cookbook* design. The shortcomings of this book are predominantly lack of organization and an ineffective attempt to provide a comprehensive manual that involves too broad a topic base.

In reviewing this text the question arises as to who might be interested in its use. It does not provide extensive enough detail to be useful to housestaff or to intensive care unit physicians. Its lack of concise organizational structure would impair its use for emergency reference, limiting its value to practicing emergency room physicians. Perhaps the answer lies in the preface where it is noted that the intent of this text is to supplemen a course in critical care. This is repeatedly borne out by the conviction at the end of many chapters that much has not been discussed. Although this may not be as great a problem to those attending the critical care symposium, it would hamper a person who has not been a participant. Consequently, one is left to conclude that this is a text probably best suited for those who attended the critical care symposium and wish to have some permanent record to supplement the proceedings.

It is conceded that there are occasional nuggets of information that are scattered intermittently throughout the text. However, one has to sift through considerable dross in the process. This text is a paradoxic blend of useful and useless information that suffers for lack of careful editing.

Admittedly, it is difficult to include extensive detail in a text with as broad a scope as attempted by the authors. However, as an example, it would seem vitally important to include problems and complications associated with flow-directed pulmonary artery catheters in the chapter discussing indications for their use. Additionally, it seems to be a poor choice to explore the relationship of pulmonary edema to hydrostatic and colloid osmotic pressures in man and base the discussion on a personal series of 26 patients, in only 14 of whom pulmonary edema developed. It is obvious that the current cardiology literature provides ample material to draw from in preparing a topic such as this.

There are particular commendable sections that should be noted. One of these is the discussion of shock lung, where organization of the material is presented in such a manner that it would be useful to critical care physicians. The chapter on acute pulmonary thromboembolism is also very well organized and well written. Similarly, the discussion of disseminated intravascular coagulation is presented in a straightforward and concise manner with a differential diagnosis of precipitating disorders. Also of value is the presentation of the principles of fluid challenge for routine management of shock. The standard fluid challenge protocol is outlined and should be very useful to critical care physicians.

Also of favorable note is the discussion of potentially fatal ventricular arrhythmias and their management with emphasis on prophylactic treatment of patients with myocardial infarction. This is a well-accepted approach and the outline of the management of such patients is well done. Similarly the discussion of impedance reduction in heart failure therapy is of timely importance. However, with the progress in this area in the current literature further updating of the information is necessary.

Other highlights of this text are the chapters on acute life-threatening fluid and electrolyte abnormalities and the metabolic causes of arrhythmias in critically ill patients. The organizational structure of the former lends itself for use in a critical care unit. A concise outline of causes, symptoms, signs and treatment is presented and is of obvious value. The latter chapter discusses the metabolic causes of arrhythmias in critically ill patients. This is a topic that needs to be stressed and should be very familiar to those responsible for the care of critically ill patients.

In summary, the title of this text is a misnomer in that it is not what one would expect from a manual. The recurring lack of organization and unfortunate brevity make it difficult to use as an emergency reference text. Its redeeming value lies in the periodic appearance of some very useful bits of information. It is only regrettable that the format does not lend itself to ready accessibility to this information.

DALE M. ISAEFF, MD
Medical Director, Intensive Coronary Care Unit
Assistant Professor of Medicine
Loma Linda University Medical Center
Loma Linda, California

in memoriam

California Medical Association

Arons, Joseph J., San Rafael. Died August 21, 1980 in San Rafael of heart disease, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1941. Licensed in California in 1941. Dr. Arons was an associate member of the Marin Medical Society.

Bailey, K. Grosvenor, Los Angeles. Died August 12, 1980 of cerebrovascular accident, aged 81. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1926. Licensed in California in 1926. MD degree from California College of Medicine, 1962. Dr. Bailey was a member of the Los Angeles County Medical Association.

Biddle, Samuel G., Seal Beach. Died February 18, 1980, aged 89. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1917. Licensed in California in 1920. MD degree from California College of Medicine, 1962. Dr. Biddle was a member of the Los Angeles County Medical Association.

Blanton, John Lee, Santa Cruz. Died September 8, 1980 in a light plane crash in Wyoming, aged 43. Graduate of the University of Tennessee School of Medicine, Memphis, 1962. Licensed in California in 1965. Dr. Blanton was a member of the Santa Cruz County Medical Society.

Burgess, Woodrow W., Davis. Died August 18, 1980, aged 66. Graduate of Duke University School of Medicine, Durham, NC, 1941. Licensed in California in 1948. Dr. Burgess was a member of the Sacramento-El Dorado Medical Society.

Burnett, Ralph W., Bakersfield. Died September 12, 1980 in Newport Beach of myocardial infarction, aged 63. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1945. Licensed in California in 1945. Dr. Burnett was past president of the California Medical Association and past president of the Kern County Medical Society.

Haworth, Kenneth W., Martinez. Died in July 1980 in Benicia, aged 68. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1936. Licensed in California in 1946. Dr. Haworth was an associate member of the Napa County Medical Society.

Lomas, Jack B., Beverly Hills. Died July 29, 1980, aged 73. Graduate of the University of Southern California School of Medicine, Los Angeles, 1934. Licensed in California in 1934. Dr. Lomas was a member of the Los Angeles County Medical Association.

Person, Douglas Allen, Santa Cruz. Died September 8, 1980 in a light plane crash in Wyoming, aged 51. Graduate of the University of Michigan Medical School, Ann Arbor, 1955. Licensed in California in 1957. Dr. Person was a member of the Santa Cruz County Medical Society.

Sharrer, Norman E., Visalia. Died August 22, 1980 in Fresno of cancer, aged 57. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1947. Licensed in California in 1956. Dr. Sharrer was a member of the Tulare County Medical Society.

Stern, Elizabeth, Los Angeles. Died August 9, 1980 of carcinoma of the stomach, aged 64. Graduate of the University of Toronto Faculty of Medicine, 1939. Licensed in California in 1941. Dr. Stern was an associate member of the Los Angeles County Medical Association.

Yurich, Eugene L., Santa Cruz. Died September 8, 1980 in a light plane crash in Wyoming. Graduate of the University of Wisconsin Medical School, Madison, 1955. Licensed in California in 1959. Dr. Yurich was a member of the Santa Cruz County Medical Society.

Washington State Medical Association

Eli, Earl Wilbur, Seattle. Died August 11, 1980, aged 70. Graduate of the University of Minnesota Medical School, Minneapolis, 1952. Licensed in Washington in 1952. Dr. Eli was a member of the King County Medical Society.

Fernandez, Lilia F., Seattle. Died August 3, 1980, aged 51. Graduate of the College of Medicine, Manila Central University, Manila, 1955. Licensed in Washington in 1970. Dr. Fernandez was a member of the Washington State Medical Association.

Frick, Wesley V., Dayton. Died August 25, 1980, aged 80. Graduate of the University of Oregon Medical School, Portland, 1931. Licensed in Washington in 1932. Dr. Frick was a member of the Walla Walla Valley Medical Society.

MacMahon, Charles E., Seattle. Died August 6, 1980, aged 70. Graduate of Harvard Medical School, Boston, 1936. Licensed in Washington in 1940. Dr. MacMahon was a member of the King County Medical Society.

Paeth, George William, Seattle. Died August 12, 1980, aged 59. Graduate of Tulane University School of Medicine, New Orleans, 1947. Licensed in Washington in 1950. Dr. Paeth was a member of the King County Medical Society.

Templeton, Frederic E., Seattle. Died in August 1980, aged 75. Graduate of the University of Oregon Medical School, Portland, 1931. Licensed in Washington in 1946. Dr. Templeton was a member of the King County Medical Society.

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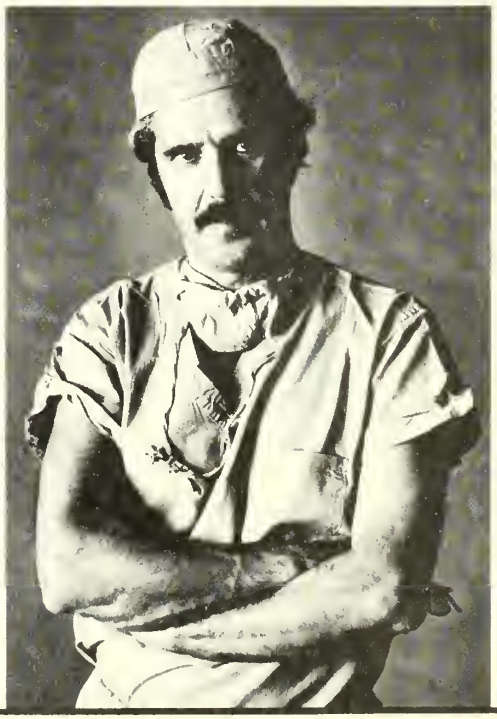

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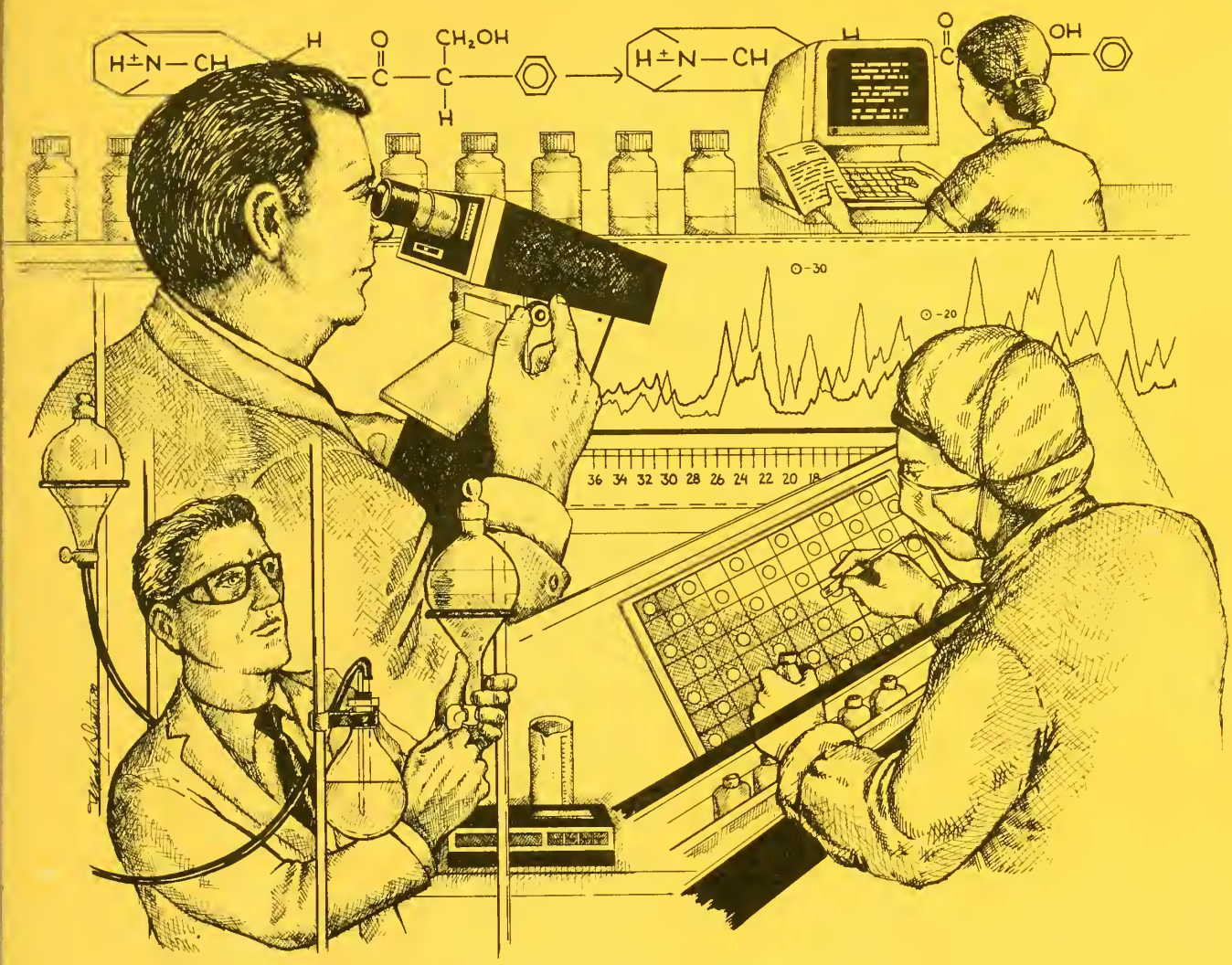

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FAMILY PRACTICE FACULTY—BOARD-CERTIFIED FAMILY PHYSICIAN wanted for full-time faculty position in accredited community-based Family Practice residency program with University affiliation. Experience in private practice as well as teaching is desirable. Good community support, good educational orientation, and nice place to live. Applications accepted until November 24, 1980. Anticipated starting date January 1, 1981. Send curriculum vitae with references to Roy H. Virak, MD, Director—Tacoma Family Medicine—A314, Allenmore Medical Center, Tacoma, WA 98405. Telephone (206) 383-5855. Equal opportunity employer.

SEEKING A LICENSED MD WITH A MASTERS OF PUBLIC HEALTH or equivalent and at least three years' experience in Public Health Administration to function as Director of Health and manage and administer a large combined City-County Health Department with a staff of 190, serving a population of approximately 470,000 and with a departmental budget of $6.7 million. Submit detailed résumé and/or write for further information to City of Tacoma Personnel Department, Room 335, County-City Building, Tacoma, WA 98402 or phone (206) 593-4250. Résumés will be accepted until a sufficient number of qualified résumés are received.

CALIFORNIA: Faculty member for Family Practice Residency Program located in Orange County. Require Residency training, Board Certified Family Physician. Practice and/or teaching experience preferred. Responsibilities include In-patient coordination of Residency Program. Salary negotiable. Program affiliated with the University of Southern California, School of Medicine. Send all inquiries and CV to: J. Blair Pace, MD, Director, Family Practice Residency Program, Santa Ana-Tustin Community Hospital, 1001 N. Tustin Ave., Santa Ana, CA 92705. Phone: (714) 835-3555.

OBSTETRICIAN/GYNECOLOGIST—Board certified/eligible Ob/Gyn wanted to join expanding multispecialty group in Santa Rosa (50 min. from San Francisco). California license, good starting salary leading to partnership, plus fringe benefits, malpractice coverage, ample vacation and education leave. Excellent working environment. Position available now. An equal opportunity, affirmative action employer. Contact: Steven Batanides, MD, Kaiser-Permanente Medical Center, 95 Montgomery Drive, Santa Rosa, CA 95404. Phone (707) 544-1330 ext. 281.

Excellent opportunities exist in prime geographical locations throughout the Western, Midwestern and Rocky Mountain states for General and Family Practice Physicians. Access to hunting, fishing, skiing, boating and other excellent recreational activities. Top school systems and warm community atmosphere. Unlimited opportunity to make an impact. Compensation package includes base guarantee, incentives and fringe benefits. Complete medical practice support. The future holds unlimited growth potential. For information contact:

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HEMATOLOGIST-ONCOLOGIST needed for busy, aggressive practice of same in Northern California community, one and a half hours from San Francisco. Teaching available. Send CV to Box 6153, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OB/GYN NEEDED in a most desirable resort community to provide OB/GYN coverage for Santa Barbara County. No overhead. Malpractice paid. Contact C. F. Schultze, MD, 3955 Laguna Blanca Dr., Santa Barbara, CA 93110.

FAMILY PRACTICE PHYSICIAN needed to share clinic. Well established practice in beautiful Southern Utah. Reply Earl Plunkett, MD, Box 489, Hurricane, UT 84737. Phone (801) 635-4688.

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INFORMATION

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PHYSICIANS WANTED

PULMONOLOGIST WANTED: Thriving, expanding community hospital in Indio, California. Currently operating without medical pulmonologist. He/she who comes will be busy. Private practice plus lab management fee. Thomas J. May, 47-111 Monroe St., Indio, CA 92201. (714) 347-6191.

GENERAL PRACTITIONER/FP—Private practice opportunity in association with acute-care general hospital in Santa Maria, California. Fully accredited CMA and JCAH with 24-hour ER. Excellent guarantee of annual gross billings, free office rent, other financial assistance available. Located within 10 miles of beaches and lakes. Interested physicians please send CV to Joyce R. Wallace, Office of Physician Relations, Summit Health Ltd., 4070 Laurel Canyon Blvd., Studio City, CA 91604.

OPHTHALMOLOGIST to join established ophthalmologist in Los Angeles area. Must be well-trained and motivated. Preferably interested in permanent association (partnership). Send CV to Box 6154, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

VIRGINIA: Primary care physician needed to join staff at growing practice in scenic central Virginia. Enjoy well equipped facility, excellent staff, strong community support, guaranteed income, excellent linkages with hospitals and other providers in area with growing economy, beautiful mountains, large lakes, year round mild weather, available land and substantially lower cost of living. Locum tenens considered. Contact: John Troidl, Administrator, Evington Medical Center, "P" Drawer 81, Evington, Virginia 24550.

FAMILY PRACTITIONER/INTERNIST—CALIFORNIA—To associate with ABFP certified family physician in city of 105,000—State Certified Lab, X-Ray, EKG. Some supervision of Physician's Ass'ts. Central Valley—close to sea and mountains. Write: Granger Avenue Medical Group, P.O. Box 4156, Modesto, CA 95352.

ASSOCIATE WANTED

FAMILY PHYSICIAN or other primary care: To associate with long-established board certified FP. Recent ultra-modern medical office in high income area of Orange County. Major hospital close by. Community college and Calif. State Univ. in area, teaching—UCI. Write Box 6155, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

POSITIONS AVAILABLE

WANTED: A nutritionally oriented physician in the San Francisco Bay Area. Must be readily available and have a California license. Salary negotiable. Contact: Carl L. Ebnother, MD, Center for Orthomolecular Medicine, 925 E. Meadow Dr., Palo Alto, CA 94303. (415) 494-7002.

SITUATIONS WANTED

PULMONARY INTERNIST, University trained, ABIM, trained all phases of pulmonary medicine; seeks practice opportunity; available July 1981. Box 6141, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST, ABIM cert., University trained, 33, interest and training in CCU, ICU. Excellent references, N. Bay Counties or Foothills area. Box 6151, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FAMILY PRACTITIONER board qualified. Licensed California, Oregon, Washington, Minnesota. Age 47. Interested in all opportunities, prefer group practice, ER work, industrial medicine, metropolitan or rural practice. Full or part time. Contact Robert L. Stein, MD, 4705 Fondulac, Muskogee, OK 74401. Telephone (918) 682-2721.

SITUATIONS WANTED

RADIOLOGIST, 50, board certified with board experience in general radiology and diagnostic ultrasound. Available for locum tenens work. Prefer Northern California. Jack Scott, MD, 11898 Forest View Dr., Nevada City, CA 95959. (916) 272-9304.

NEPHROLOGIST INTERNIST, 31, ABIM certified, seeks associateship or group practice opportunity in coastal community. Available July, 1981. Reply Box 6149, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, 49, certified AP-CP, broad experience and excellent references, California and Oregon licenses. Available immed. (714) 287-5539.

LOCUM TENENS WORK WANTED

FAMILY PHYSICIAN, ABFP, mature, broad office experience, med. school faculty appt. available for locum tenens work in Los Angeles, San Diego or Palm Springs areas. (303) 377-9373.

OFFICE FOR LEASE OR RENT

SANTA ANA, CA—Space available to share allergist office, for Allergist or Internist in established medical center. J. Newland, MD, Suite 202, 1125 E. 17th St., Santa Ana, CA 92701. (714) 834-1414.

WEST VALLEY'S FINEST MEDICAL—Prestigious medical suites available on Balboa Blvd. with easy freeway access, ranging from 659 to 1,530 sq. ft. Newly redesigned complex. Facilities include restaurant, pharmacy, surgical supply and swimming pool with sauna. Next door to newly remodeled full service hospital. Call Patricia Kershaw, (213) 986-8100.

MEDICAL PRACTICES AVAILABLE

BUYING or SELLING any type Medical Practice contact California Professional Practices, 2555 Huntington Dr., Suite D, San Marino, CA 91008. (213) 796-9262 or Agent Mr. Reilly (805) 543-4782 or Cliff Rauch (714) 997-0853.

PRACTICES FOR SALE

Fourteen years experience as professional brokers of medical practices throughout California. Buyers: request to be placed on free mailing list of practices available. Sellers: call in regards to services. 100% financing available for any of our practices. **Professional Practice Sales, 1428 Irving Street, San Francisco, CA 94122, (415) 661-0700, or 364 East First Street, Tustin, CA 92680, (714) 832-0230.**

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January 9-10, 1981

San Jose, California

TRAUMA and CANCER

Speakers:

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George Block — Arthur Donovan
Gerald Shafton — Josef Fischer

Meeting Fee: $175

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INTERNAL MEDICINE PRACTICE available immediately, located in lovely Southwestern Oregon, excellent opportunity to assume large stimulating practice. Active, sophisticated medical community. Equipment and office furniture available. R. K. Gundry, MD, 691 Murphy Rd., Suite 106, Medford, OR 97501. Telephone (503) 779-9285.

PROFESSIONAL PRACTICE OPPORTUNITIES—Dermatology-Internal-Ophth-Family-others avail. To Buy or Sell any type practice, or for placement contact Mary Bradshaw, 21 Altamount, Orinda, CA 94563. (415) 376-0762.

MORGAN HILL—SANTA CLARA COUNTY: Excellent opportunity for a young medical group eager to start practice in a rapidly growing community. Busy GP practice (Medical Clinic) in temporary quarters. For sale due to health and personal problems. 1.5 acre with city-approved use permit for a new medical complex and a coffee shop with building plans. Low down payment. Owner will assume. Centrally located 20 miles south of San Jose and 35 miles to Carmel/Monterey. Location equidistant to two big hospitals. Area is excellent place to live and practice. Contact: Mrs. Laurel, phone: (408) 578-2120, 779-2164.

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JUNE 21-26, 1981

Directed by

CHARLES B. CARRINGTON, MD
and
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For its 19th edition, this course will be conducted for the first time at **Stanford Medical Center in Palo Alto.** This broad survey of the pathology of adult pulmonary disease is planned for pathologists and for other physicians who have a special interest in lung disease. It includes lecture-slide demonstrations and microscopy laboratories. Some experience in the interpretation of microscopic tissue is a prerequisite for maximum benefit. Registration is limited to 40 persons. Tuition is $550. Approved for 50 hours of Category I CME credit.

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Remember when you were a struggling medical student? It was tough. But medical students today have an even tougher time financing their medical education. Interest rates are exorbitant and loan guarantee programs are continually reducing their commitments.

The California Medical Education and Research Foundation has initiated a low-interest loan program to help medical students. Physicians have been asked to contribute, on a voluntary basis, $100 a year for each of three years to develop the loan program.

Response has been significant: one foundation for medical care (San Bernardino) contributed $10,000; one county medical society (Solano) contributed $1,000 and approximately 150 physicians contributed from $100 to $300 each.

But CMERF is still woefully short of enough money to implement a rational program to meet the demand. The situation is still serious. Interest rates remain too high for medical students to afford. And the two major national loan guarantee programs have either suspended operations or have greatly curtailed them.

Please respond to the urgent need by sending your $100 tax-deductible contribution to our nonprofit foundation. Support a student. Send your contribution to CMERF, 731 Market Street, San Francisco, CA 94103.

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This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

December 12-14—**Anesthesia: Before and After.** Tucson Hospitals Medical Education Program at Canyon Hotel, Palm Springs. Friday-Sunday. $150. Contact: James P. Angiulo, MD, Kino Community Hosp., 2800 E. Ajo Way, Tucson, AZ 85713.

January 6-10—**Anesthesia Update.** UCSD at Hotel del Coronado, Coronado. Tuesday-Saturday. 20 hrs. $250.

January 23-25—**Pediatric Anesthesiology—19th Clinical Conference.** Childrens Hospital of Los Angeles at Marriott Hotel, Los Angeles. 15 hrs. $165. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 14-21—**9th Obstetric Anesthesia Conference.** Ohio State Univ. at Sheraton Waikiki, Honolulu. One week. 25 hrs. Contact: Excursions Unlimited, Inc., c/o OSU Dept. of Anesthesiology, 1820 Northwest Blvd., Columbus, OH 43212. (800) 848-4438.

April 1-5—**S.O.A.P.** UCSD at Vacation Village, San Diego. Wednesday-Sunday.

CANCER

November 15—**Current Advances in Cancer Care.** Eden Hospital and American Cancer Society, Alameda Chapter, at Hilton Hotel, Oakland. Saturday. Contact: Joseph C. Beck, MD, Dept. of Radiology, Eden Hosp., 20103 Lake Chabot Rd., Castro Valley 94546. (415) 537-1234, ext. 252.

November 21—**Modern Management of Anorectal Carcinoma.** USC Cancer Center and American Cancer Society at Bonaventure Hotel, Los Angeles. Friday. Contact: Robert J. McKenna, MD, Dir., USC Comprehensive Cancer Ctr., 1721 Griffin Ave., Los Angeles 90031. (213) 226-4041.

December 10—**16th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Memorial Hosp., 5th Ave. and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

January 22-24—**Current Concepts in Cancer Diagnosis.** UCLA at Century Plaza Hotel, Los Angeles. Thursday-Saturday.

January 23-24—**Cancer Update 1981.** Peralta Hospital at Goodman's Hall, Jack London Square, Oakland. Friday-Saturday. 10 hrs. Contact: Susan Ford, Education and Training Dept., Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 2327.

January 24-25—**Current Approaches to Radiation Oncology.** UCSF at Sir Francis Drake Hotel, San Francisco. Saturday-Sunday.

January 30-February 1—**Midwinter Oncology Conference—for Radiation Oncologists.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $150. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

February 5-9—**Controversies in Lung Cancer.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Monday. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** See Medicine, February 23-26.

February 25—**Ovarian Cancer.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

February 28-March 1—**Recent Advances in Cancer Diagnosis.** UCLA. Saturday-Sunday.

March 6-8—**Current Approaches to Radiation Oncology, Biology and Physics.** See Radiology, March 6-8.

March 13-14—**Childhood Cancer: Triumph Over Tragedy—16th Annual Cancer Symposium.** West Coast Cancer Foundation and Calif. Division of American Cancer Society at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. $110 before February 1; $130 thereafter. Contact: WCCF, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

EMERGENCY MEDICINE

November 20—**Clinical Pharmacology in the Emergency Department.** UCSD at University Hospital, San Diego. Thursday. 2 hrs. CMA and ACEP. $10. Contact: John Fredericks, MD, 6757 Heath Ct., Carlsbad 92008. (714) 438-5377.

December 8-12—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

December 10—**Emergency Medicine.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

January 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

January 21-23—**Sierra Traumatological Society.** See Surgery, January 21-23.

January 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

February 16-19—**Emergency Medicine: New Concepts in Resuscitation.** UCD at Hyatt Lake Tahoe, Incline Village. Monday-Thursday. 19¼ hrs.

February 16-20—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

March 8-14—**2nd Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Mountain. One week. 25 hrs. $290. Contact: Daniel Abbott, MD, P.O. Box 52-B, Newport Beach 92662. (714) 642-7080.

March 23-27—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

April 18-25—**Emergency Medical Care.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

April 25-May 2—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui. One week. $350.

MEDICINE

November 17-19—**International Symposium on Status Epilepticus.** UCLA at Miramar-Sheraton, Santa Monica. Monday-Wednesday. 20 hrs.

November 19—**10th Annual Gastroenterology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. Contact: Cont. Med. Ed., N. T. Enloe Memorial Hospital, 5th Ave. and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

November 21-22—**Advances in the Diagnosis and Management of Liver Disease.** Huntington Memorial Hospital at Huntington Sheraton Hotel, Pasadena. Friday-Saturday. 8 hrs. Contact: Mrs. Arlene M. Ellis, Coordinator, Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105. (213) 440-5165.

November 29-December 1—**Advances in Heart Disease 1981.** American College of Cardiology at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 1-3—**Cardiovascular-Pulmonary Update for the Practicing Physician.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 19 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

December 5—**Recognition and Management of Bleeding Disorders.** Children's Hospital Medical Center of Northern Calif. at Sir Francis Drake Hotel, San Francisco. Friday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

December 5-7—**Cardiac Rehabilitation.** International Medical Education Corp. at Wilshire Hyatt, Los Angeles. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

December 5-7—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Desert Inn, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8646.

December 6-7—**Neurology for the Primary Care Physician.** UCLA. Saturday-Sunday.

December 10—**Collagen Disease—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $30.

December 11-14—**Intensive Care for Neurological Trauma and Disease: A New Decade.** Comprehensive Central Nervous System Injury Foundation and Univ. of Miami at Vacation Village, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Comprehensive CNS Injury Fndn., P.O. Box 9494, San Diego 92109.

December 13—**Endocrinology and Metabolism in the 80's: A New Frontier.** Daniel Freeman Hospital Medical Center at Hyatt House, Los Angeles. Saturday. 6 hrs. $100. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp. Med. Ctr., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 3427.

December 14-20—**Immunohematology: New Concepts in Clinical Application.** Univ. of Pennsylvania School of Medicine and International Center for Health Education at Kauai Surf Hotel, Kauai, Hawaii. One week. Contact: Internat'l Health Resource Ctr. of Hawaii, P.O. Box 3109, Lihue, Kauai, Hawaii 96766. (808) 245-2121.

January 9-11—**Debates, Controversies and Concepts in the Treatment of the High Risk Patient.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Friday-Sunday. 19 hrs. $225. Contact: Lore Kahane, Rm. 2049, Cedars-Sinai Med. Ctr., P.O. Box 48750, Los Angeles 90048. (213) 855-5547.

January 10-11—**Practical Pulmonary Diseases.** UCLA. Saturday-Sunday.

January 14—**Arrhythmias—Their Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $30.

January 23-24—**2nd Clinical Conference on Congenital Heart Disease.** Childrens Hospital of Los Angeles at Biltmore Hotel, Los Angeles. Friday-Saturday. 12 hrs. Contact: Bernard L. Tucker, MD, 1136 W. 6th St., Los Angeles 90017.

January 24—**Cardiology Seminar—10th Annual.** Fresno Community Hospital and Medical Center. Saturday. Contact: Joann Ellis, Ed. and Training Dept., Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

January 26-28—**Practical Management of Bronchial Asthma.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

January 30-31—**Cardiology Update — 1981 — The Changing Scene.** St. Francis Medical Center at Bonaventure Hotel, Los Angeles. Friday-Saturday. 14 hrs. Contact: Allan Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603- 6174.

February 2-4—**Clinical Echocardiography—1981.** American College of Cardiology at Sheraton Harbor Island Hotel, San

Diego. Monday-Wednesday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 4—**Endocrine Disorders.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

February 4-6—**Children With Heart Disease.** USC at Gene Autry Hotel, Palm Springs. Wednesday-Friday. 14 hrs.

February 4-6—**Western Section of the Society for Investigative Dermatology, Western Section of American Federation for Clinical Research, Western Society for Clinical Research.** Carmel. Wednesday-Friday. Contact: Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, NJ 08086.

February 11-13—**Recent Advances in Neurology.** UCSF. Wednesday-Friday.

February 14—**Sixth Annual Liver Conference: Cirrhosis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 16-18—**Recent Advances in Clinical Endocrinology.** UCSF at Sir Francis Drake Hotel, San Francisco. Monday-Wednesday.

February 18-20—**Neuro-Orthopedic Screening.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 18-April 22—**Gastroenterology.** UCLA. Wednesday evenings.

February 19-21—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Fndn., American Heart Assn., American Lung Assn., Nat'l Critical Care Institute of Education, Vascular Disease Fndn. at Mission Bay Hilton, San Diego. Thursday-Saturday. $250. Contact: CREF, P.O. Box 33185, San Diego 92103.

February 19-22—**Federation of Western Societies of Neurological Science.** Stanford Court, San Francisco. Thursday-Sunday. Contact: Grant E. Gauger, MD, 1411 E. 31st St., Oakland 94602.

February 21—**Workshop in Advanced Electrocardiography.** PMC. Saturday. 7 hrs. $110.

February 21-28—**Metabolism and Endocrinology.** Univ. of Washington School of Medicine at Kona Surf Hotel, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 21-28—**Practical Neurology.** Univ. of Washington School of Medicine at Ilikai Hotel, Honolulu. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** Scripps Clinic and Research Fndn. at Vacation Village, San Diego. Monday-Thursday. 25 hrs. $290. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 25—**Hospital Acquired Infections.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 2-4—**Dermatology for Internists.** STAN at Eisenhower Medical Center, Rancho Mirage. Monday-Wednesday.

March 2-4—**Immunology.** STAN. Monday-Wednesday. 13 hrs. $225.

March 2-4—**Basic Neuroscience and Biobehavioral Science.** See Psychiatry, March 2-4.

March 4-7—**Immunology and Clinical Practice of Allergy—5th Annual Course.** UCSD at Hilton, San Diego. Thursday-Saturday. 20 hrs.

March 6—**8th Annual Diabetes Program.** UCD at Red Lion Motor Inn, Sacramento. Friday. 6½ hrs.

March 7-11—**American Academy of Allergy.** Hilton Hotel, San Francisco. Saturday-Wednesday. 32 hrs. $125, nonmembers. Contact: Donald McNeil, Exec. Dir., AAA, 611 E. Wells St., Milwaukee, WI 53202. (414) 272-6071.

March 8-11—**Consultants' Course in Dermatology.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

March 13-14—**Diagnosis and Treatment of Venous Thromboembolism.** PMC. Friday-Saturday. 10 hrs. $125.

March 15-19—**American College of Cardiology.** San Francisco. Sunday-Thursday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 15-20—**Symposium on Gastroenterology.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Friday.

March 23-April 4—**Intensive Review of Internal Medicine—29th Annual.** USC. Two weeks.

April 5-8—**Cosmetics for the Clinician: A Symposium for Dermatologists.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

April 6-15—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 8—**Cardiology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Memorial Hosp., 5th Ave and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

April 8—**Annual Physicians' Cardiovascular Symposium.** American Heart Assn., Central Valley Chapter, at Hilton, Fresno. Wednesday. Contact: Genny Berry, AHA, Central Valley Chap., 3835 N. West Ave., Fresno 93705. (209) 224-8215.

April 8-10—**Update in Pediatric Pulmonary and Intensive Care.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 8-11—**California Blood Bank System—29th Annual Meeting.** Hyatt Airport Hotel, Los Angeles. Wednesday-Saturday. Contact: Mrs. Beverley Hayhurst, Exec. Sec., CBBS, P.O. Box 5401, San Bernardino 92412. (714) 885-6503.

OBSTETRICS AND GYNECOLOGY

December 5-7—**5th Annual Symposium on Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort. Friday-Sunday. 18 hrs. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 10-16—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

January 14-17—**Postgraduate Course on Basic and Advanced Gyn Urology: Theory and Practice.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Wednesday-Saturday. 20 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 25-30—**Obstetrics-Gynecology Update: 1981.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

January 26-30—**10th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday. 36 hrs. $400.

February 7-8—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. Contact: Dee Davis, Exec. Sec., LAOGS, 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

April 4-11—**Current Concepts in Ob/Gyn.** Univ. of Washington School of Medicine at Kona Surf Hotel, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 10-11—**26th Annual T. Hart Baker, MD, Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at South Coast Plaza Hotel, Costa Mesa. Friday-Saturday. Contact: Lilia M. Guerrero, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

PEDIATRICS

November 15—**Pediatric Ophthalmology for the Primary Care Physician.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 4 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

November 17-December 8—**New Directions in the Care for the Handicapped Child.** American Academy of Pediatrics, Calif. Chap. III, at Children's Hospital, San Diego. Mondays; 6:00-10:00 p.m. Contact: Harold M. Sterling, MD, Dir. of Rehabilitation, Children's Hosp. and Health Center, 8001 Frost St., San Diego 92123. (714) 292-3478.

November 21-24—**Pediatric Update.** American Academy of Pediatrics, Calif. Chapters 1, 2 and 3, at Hilton Hotel, Las Vegas. Friday-Monday. 15 hrs. $175, members; $200, nonmembers. Contact: AAP, Chap. 2, P. O. Box 2134, Inglewood 90305.

December 3-7—**5th Annual Pediatric Seminar.** Los Angeles Pediatric Society at Kahala Hilton, Honolulu. Wednesday-Sunday. 11 hrs. $75. Contact: Los Angeles Pediatric Soc., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

December 5-7—**Children and Their Skeletons: A Practical Approach.** UCD at Hyatt Del Monte, Monterey. Friday-Sunday.

February 4-6—**Children With Heart Disease.** See Medicine, February 4-6.

April 3-4—**Pediatric Topics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 8-10—**Update in Pediatric Pulmonary and Intensive Care.** See Medicine, April 8-10.

PSYCHIATRY

November 17-21—**Group Therapy.** UCSF. Monday-Friday.

November 22—**Family Interventions as an Alternative to Psychiatric Hospitalization.** Mental Research Institute, Palo Alto. Saturday. 7 hrs. $50. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 23-30—**New Directions in Psychiatry.** Univ. of Washington School of Medicine at Ilikai Hotel, Honolulu. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

January 14-May 27—**Practicum on Family Therapy and Schizophrenia.** Mental Research Institute, Palo Alto. Wednesdays. 80 hrs. $600. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 25-31—**7th Annual Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. One week. 26 hrs.

January 30-31—**Heinz von Foerster on Cybernetics, Language, and Understanding.** Mental Research Institute, Palo Alto. Friday-Saturday. 12 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

March 2-4—**Basic Neuroscience and Biobehavioral Science.** STAN. Monday-Wednesday. 15 hrs. $225.

April 3-5—**Cults, Religiosity and the Adolescent.** UCSF. Friday-Sunday.

RADIOLOGY AND PATHOLOGY

December 13-14—**Using the Clinical Lab.** UCLA. Saturday-Sunday.

January 19-23—**Interventional Radiologic Techniques: Computed Tomography and Ultrasonography.** UCSF at Fairmont, San Francisco. Monday-Friday. $350.

January 19-24—**Review Course in Clinical Ob, Gyn, and Histological Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Monday-Saturday. 41 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 21-23—**8th Annual Postgraduate Course in Genitourinary Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 22½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 24-31—**International Diagnostic Radiology Conference.** UCSF at Maui Surf Hotel, Maui, Hawaii. One week.

January 26-30—**Tumorous Conditions of the Bones and Soft Tissues.** American Society of Clinical Pathologists at San Diego. Monday-Friday. 37½ hrs. $500, ASCP members; $600, nonmembers. Contact: Admin. Asst., Education Ctr., ASCP, 2100 W. Harrison St., Chicago 60643. (312) 738-1336.

January 30-February 1—**33rd Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $150. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

February 4-6—**Recent Progress in Diagnostic Laboratory Immunology.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 24 hrs. $250. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 9-12—**Molecular Basis of Cell-Cell Interaction.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Monday-Thursday. 24 hrs. $165. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 11—**Neuroradiology—Its Use, Indications and Values in Strokes, Tumors and Head Trauma.** LLU. Wednesday. 4 hrs. $30.

February 18-20—**Anaerobic Bacteriology Methods.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 15 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 25-27—**Minicomputers, Microcomputers and Big Computers.** American Society of Clinical Pathologists at Monterey. Wednesday-Friday. 19½ hrs. Contact: Admin. Asst., Education Center, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

February 27-March 1—**Neuroradiology.** USC. Friday-Sunday. 20 hrs. $200.

March 4-7—**Sierra Radiology Conference—2nd Annual.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at North Lake Tahoe. Wednesday-Saturday. 18 hrs. $245. Contact: Michael H. Reid, PhD, MD, Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

March 6-8—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Friday-Sunday.

March 9-13—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $350.

March 13-19—**College of American Pathologists/American Society of Clinical Pathologists—Joint Spring Meeting.** Town and Country, San Diego. Friday-Thursday. Contact: Joan Lipe, CAP, 7400 N. Skokie Blvd., Skokie, IL 60077. (312) 677-3500.

March 14-15—**B-Scan Ultrasonography: Update.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

April 11-18—**Hawaii Imaging Conference.** American College

of Medical Imaging at Kauai Surf Hotel, Kauai, Hawaii. One week. 23½ hrs. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

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SURGERY

December 3-4—**6th Annual Meeting and Scientific Symposium —Lyman A. Brewer, III, International Surgical Society—Controversies in the Management of Coronary Heart Disease.** White Memorial Medical Center at Hilton, Los Angeles. Wednesday-Thursday. Contact: Dr. Howard Whigham, Dir., Research and CME, White Mem. Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 263-6100.

December 6—**Practical Workshop on Surgery of the Eyelids, Lacrimal System and Orbit.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $275. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

December 11-13—**Trauma.** No. Calif. Chap of the Committee on Trauma of Am. College of Surgeons at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. Contact: Donald D. Trunkey, MD, Chief of Surgery, S.F. Gen. Hosp., 1001 Potrero Ave., San Francisco 94110.

December 11-14—**Intensive Care for Neurological Trauma and Disease: A New Decade.** See Medicine, December 11-14.

December 12-13—**Ophthalmology Update.** UCD, UCSF, PMC, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

January 9-11—**Debates, Controversies and Concepts in the Treatment of the High Risk Patient.** See Medicine, January 9-11.

January 10—**Photocoagulation Therapy.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

January 21-23—**Sierra Traumatological Society—10th Annual Meeting.** Bear Valley. Wednesday-Friday. 6 hrs. Contact: Sierra Traumatological Soc., P.O. Box 230, Stockton 95201. (209) 466-9535.

January 23-24—**Third Annual Postgraduate Course in Surgery.** UCD at Point West Hotel, Sacramento. Friday-Saturday. 14 hrs. $85.

January 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

January 25-28—**Society of Thoracic Surgeons—17th Annual Meeting.** Bonaventure Hotel, Los Angeles. Sunday-Wednesday. Contact: W. G. Purcell, Bus. Mgr., STS, 111 E. Wacker Dr., Chicago 60601.

January 25-30—**Assembly in Surgery—4th Annual.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sunday-Friday. 28 hrs.

February 4-6—**Current Thinking in the Management of Ocular and Adnexal Tumors.** UCSF. Wednesday-Friday.

February 5-7—**Aesthetic Rhinoplasty and Nasal Reconstruction.** UCLA. Thursday-Saturday.

February 6-8—**National Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery and American Society for Dermatologic Surgery at Ramada Inn, Beverly Hills. Friday-Sunday. Contact: Drs.

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Richard Fleming, Toby Mayer, Peter Goldman, 9730 Wilshire Blvd., Ste. 216, Beverly Hills 90212.

February 8-10—**The Mandible: Surgical Treatment of Congenital and Acquired Deformities.** UCLA. Sunday-Tuesday.

February 14-20—**Neurological Surgery of the Ear and Skull Base—3rd International Workshop.** Ear Research Institute at Newporter Inn, Newport Beach. One week. 32 hrs. $500. Contact: Derald E. Brackmann, MD, Neurological Workshop, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

February 19-21—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** See Medicine, February 19-21.

February 23-25—**American Society for Surgery of the Hand—36th Annual Meeting.** Las Vegas. Monday-Wednesday. Contact: ASSH, 2600 S. Parker Rd., Suite 132, Aurora, CO 80014. (303) 755-4588.

February 26-March 3—**American Academy of Orthopaedic Surgeons.** Convention Center, Las Vegas. Thursday-Tuesday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

March 5-7—**Calculi.** American Urological Association at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: AUA, Office of Education, Texas Med. Ctr., 4th Fl-Inst. of Religion Bldg., 1129 Wilkins, Houston, TX 77030.

March 6-7—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 11—**Common Fractures and Joint Injuries.** LLU. Wednesday. 4 hrs. $30.

March 21-22—**ECG Course for Oral and Maxillofacial Surgeons.** UCSF. Saturday-Sunday.

March 25-28—**4th Annual U.S. IOL Symposium.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Wednesday-Saturday. Contact: Debbi Miller, Dir. of Mtg. Services, Am. Intra-Ocular Implant Soc., P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

March 26-29—**Pediatric Surgery of the Head and Neck: A Frontier Symposium.** The Institute for Medical Education and Research and UCSD at Silverado Country Club and Resort, Napa Valley. Thursday-Sunday. 20 hrs. Contact: The Institute for Medical Education and Research, 135 Dickinson St., San Diego 92103.

April 8—**Urology.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

April 8-11—**Facial Plastic Surgery Symposium.** UCSF. Wednesday-Saturday.

April 9-10—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 9-11—**General Surgery.** UCSF. Thursday-Saturday.

April 23-24—**XII Jules Stein Lecture and Annual Postgraduate Seminar—Anterior Segment Disease: Current Update on Immunology, Corneal Disease, Refractive Surgery, and Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

April 25—**Radial Keratotomy Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

OF INTEREST TO ALL PHYSICIANS

November 15—**Criteria for Evaluating Pseudoscience, Cults and Holistic Medicine.** San Jose State University. Saturday. 8 hrs. $40. Contact: Susan M. Grube, MPH, Cont. Ed., San Jose State Univ., Washington Sq., San Jose 95192. (408) 277-3778.

November 15-16—**Fourth Annual National Symposium on Aging.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: Cont. Ed. Health Sciences, UCSF, 24 Kirkham, San Francisco 94143. (415) 666-3904.

November 16—**Frontiers in Medicine—12th Annual Symposium.** UCLA and Granada Hills Community Hospital at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344.

November 17-18—**The Medical Consequences of Nuclear Weapons and Nuclear War.** UCSF and Physicians for Social Responsibility at War Memorial Veterans Bldg., San Francisco. Monday-Tuesday. 11 hrs. $75. Contact: Physicians for Social Responsibility, P.O. Box 144, Watertown, MA 02172. (617) 924-3568.

November 21-23—**Sports Medicine: The Physician and the Athlete.** UCD at Marriott Inn, Berkeley. Friday-Sunday. 12 hrs. $140.

November 21-25—**Gerontological Society—Annual Scientific Meeting.** Town and Country Hotel, San Diego. Friday-Tuesday. Contact: Dr. Eugene J. Towbin, VA Hospital, Little Rock, AR 72206.

December 4—**Nutritional Aspects of Aging in America.** STAN. Thursday. 6 hrs. $40.

December 5-7—**Human Sexuality.** Cypress Foundation and UCSF at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Robert S. Meyer, Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

December 6-7—**Second Annual Patient Education Research Seminar.** UCSF. $100. Contact: Cont. Ed. in Health Sciences, UCSF, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

December 13—**Ophthalmology for the Primary Care Physician.** UCD at Holiday Inn of Sacramento Northeast. Saturday. 7 hrs.

December 13—**Diagnosis and Treatment of Sleep Disorders Patients.** STAN at Holiday Inn Holidome, Sacramento. Saturday. 7 hrs. $35.

January 9-10—**New Concepts in Management of Chronic Pain.** Bay General Community Hospital at Half Moon Inn, Shelter Island, San Diego. Friday-Saturday. 10 hrs. $45. Contact: Karen Johnson, Bay Gen. Community Hosp., 435 H St., Chula Vista 92010. (714) 420-8182.

January 14—**Sexual Therapy.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Memorial Hosp, 5th Ave and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

January 17—**The Myths and Realities of Genital Herpes: What Patients Need to Know.** UCLA. Saturday. 5 hrs. $25.

January 22-24—**Modern Drug Therapy.** STAN. Thursday-Saturday. 15 hrs. $225.

January 23—**Diagnosis and Treatment of Sleep Disorders Patients.** STAN at Marriott, Santa Clara. Friday. 7 hrs. $35.

January 26-31—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. One week. 50 hrs. Contact: Cont. Ed. in Health Sciences, UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

February 11-13—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Wednesday-Friday. 22 hrs. $275.

February 19-22—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Thursday-Sunday. 14 hrs.

February 20-21—**Pain: New Approaches to Treatment.** Mesa Vista Hospital and Vista Hill Foundation at Hotel del

Coronado, Coronado. Friday-Saturday. Contact: Virginia Everett, Vista Hill Fndn., 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 23-27—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $295.

February 26-27—**Therapeutic Drug Monitoring.** PMC. Thursday-Friday. 12 hrs. $85.

March 1-5—**Medical Evaluation of the Preoperative Patient.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Thursday.

March 5-8—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Thursday-Sunday.

March 5-8—**Sports Medicine.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday.

March 13-15—**Clinical Management.** STAN at The Lodge, Pebble Beach. Friday-Sunday. 8 hrs.

March 13-18—**California Medical Association—110th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 16-20—**Sports Medicine.** University of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $230. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 16-27—**Intensive Residency in Occupational Medicine, Session II.** UCSF. Two weeks.

March 18-20—**Recent Advances in Clinical Nutrition.** UCSD at Vacation Village, San Diego. Wednesday-Friday. 17 hrs.

April 8—**Psychiatry for the Non-Psychiatrist.** LLU. Wednesday. 4 hrs. $30.

April 11-12—**Nutrition for the Primary Care Physician.** UCSF. Saturday-Sunday. 14 hrs. $125.

April 11-18—**Office Management of Chronic Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 11-18—**Drug Therapy.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 23-25—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 23-26—**Wound Management Workshop.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

April 25-26—**Pharmacokinetics '81.** Memorial Hospital Medical Center—UCI Center for Health Education, Long Beach. Saturday-Sunday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 25-May 2—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $350.

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Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

December 11—**Women, Violence and Sexuality—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatry Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

January 28—**Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

February 5—**Endorphins—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 19—**Right Brain Functioning—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 25—**Gardnerella Vaginalis Vaginitis—Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

April 30—**Group Therapy—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

May 27—**Univ. of Wash. Ob/Gyn Session** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

June 18—**Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

November 19—**Congenital Defects—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

November 19—**Medical Oncology—Univ. of Wash. Internal Medicine Review Sessions.**

November 19, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

November 20, Thursday, Billings. 7-9:30 a.m. Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

November 21, Friday, Missoula. 8-10:30 a.m. St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

December 10—**Endocrinology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 10-12—**Pain—Univ. of Wash. Internal Medicine Review Sessions.**

December 10, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 11, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

December 12, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

January 21-25—**Sexually Transmitted Diseases—Univ. of Wash. Internal Medicine Review Sessions.**

January 21, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

January 22, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

January 23, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 11—**Pediatric Anesthesiology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 18-20—**Adolescent Medicine—Univ. of Wash. Internal Medicine Review Sessions.**

February 18, Wednesday, Great Falls. 5-7:30 p.m. Deaconess Hospital. Contact F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 19, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

February 20, Friday, Missoula. 8-10:30 a.m. St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 6-7—**Topics in Internal Medicine.** Big Sky. Friday-Saturday. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. 406) 657-7083.

March 25-27—**New Developments in Cardiology—Univ. of Wash. Internal Medicine Review Sessions.**

March 25, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 26, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 27, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 22-24—**Congenital Heart Disease in Adults—Univ. of Wash. Internal Medicine Review Sessions.**

April 22, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 23, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

April 24, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 27-29—**Office Endocrinology—Univ. of Wash. Internal Medicine Review Sessions.**

May 27, Wednesday, Great Falls. 5-7:30 p.m. Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

May 29, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 10—**Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

IDAHO

November 18—**Pulmonary Disease—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

January 20—**Endocrinology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

February 14-21—**Perinatal Critical Care.** Sun Valley. Saturday-Sunday. Elkhorn Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21-28—**Sports Medicine.** Sun Valley. Saturday-Satururday. Elkhorn Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 16—**Gyn Oncology—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

March 17—**Infectious Diseases—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 18—**Evaluation and Treatment of Premature Labor—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 19—**Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland, OR 97227. (503) 280-3200.

29th ANNUAL INTENSIVE REVIEW OF INTERNAL MEDICINE

USC

School of Medicine

MARCH 23—APRIL 3, 1981

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For information about subscribing to The Western Journal of Medicine see page 22.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 9-13—**Twelfth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

November 21—**Practical Applications of Ultrasound Scanning to Problems of Clinical Obstetrics.** Portland. Friday. Jantzen Beach Red Lion. Contact: Division of Continuing Medical Education. University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION as required by the Act of August 12, 1970; Section 3685, Title 39, United States Code, for THE WESTERN JOURNAL OF MEDICINE, published monthly at San Francisco, California, for September, 1980.

1. Location of known office of publication: 731 Market Street, San Francisco, California 94103.

2. Location of the headquarters or general business office of the publisher: 731 Market Street, San Francisco, California 94103.

3. Publisher: California Medical Association, 731 Market Street, San Francisco; Editor, Malcolm S. M. Watts, M.D., 731 Market Street, San Francisco; Managing Editor, David Greer, 731 Market Street, San Francisco.

4. Owner: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given.) California Medical Association, 731 Market Street, San Francisco, California (an unincorporated association).

5. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: There are no bondholders, mortgagees, or other security holders.

6. Paragraphs 4 and 5 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting, also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner. Names and addresses of individuals who are stockholders of a corporation which itself is a stockholder or holder of bonds, mortgages or other securities of the publishing corporation have been included in paragraphs 4 and 5 when the interests of such individuals are equivalent to 1 percent or more of the total amount of the stock or securities of the publishing corporation.

7. Average number of copies each issue during preceding 12 months: Total, 41,277; paid circulation by mail subscription, 40,329; sales through dealers and carriers, street vendors and counter sales, 0; free distribution (including samples) by mail, carrier or other means, 276; total distribution, 40,605; office use, leftover, unaccounted, spoiled after printing, 672; total net press run, 41,277. Single issue nearest to filing date, September, 1980: Total 42,345; paid circulation by mail subscriptions, 41,287; sales through dealers and carriers, 0; free distribution (including samples) by mail, carrier or other means, 396; total distribution, 41,683; office use, leftover, unaccounted, spoiled after printing, 662; total net press run, 42,345. David Greer, Managing Editor.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

November 17-20—**Immunology-Allergy.** Tacoma. Monday-Thursday. Tacoma General Hospital. Contact: CME Pierce County.

November 18—**Congenital Defects—U/W Pediatrics Sessions** (Spokane). Tuesday. 12:00-1:00 p.m. Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

November 21—**Movement Disorders.** Seattle. Friday. U/W at Museum of History & Industry. Contact: U/W School of Medicine.

November 22-29—**Financial Planning for Physicians.** Maui, Hawaii. Saturday-Saturday. U/W at Maui, Wailea Beach. Contact: U/W School of Medicine.

November 23-30—**New Directions in Psychiatry.** Honolulu, Hawaii. Sunday-Sunday. U/W at The Ilikai, Honolulu. Contact: U/W School of Medicine.

November 24—**Medical Genetics—U/W Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wentachee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

December 3—**Hyperalimentation.** Seattle. Wednsday. Northwest Hospital Auditorium. Contact: Marilyn R. Carlson, Departmental Assistant, Education and Training Dept., Northwest Hospital, 1511 North 120th, Seattle, WA 98133. (206) 364-0500.

December 4-5—**The Physician, Trustee, and Hospital.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

December 5—**The Cancer Program In Your Community Hospital.** Seattle. Friday. Doubletree Inn. Contact: Donal Sparkman, MD, Washington Division, American Cancer Society, 2120 First Avenue North, Seattle, WA 98109. (206) 283-1152.

December 5—**Specialty Problems in Pediatrics.** Seattle, Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

December 6—**The Nervous System for Attorneys.** Seattle. Saturday. Contact: U/W School of Medicine.

December 9—**Pediatric Endocrinology—U/W Pediatrics Sessions** (Spokane). Tuesday. 12:00-1:00 p.m. Sacred Heart Medical Center: Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

December 11-12—**Aging and Elderly.** Seattle. Thursday-Friday. U/W at Washington Athletic Club, Noble Room. Contact: U/W School of Medicine.

December 16—**Evaluation of Male Fertility—U/W OB-GYN Sessions** (Spokane). Tuesday. 12:00-1:00 p.m. Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD W. 101 8th Avenue, Spokane, WA 99204. (509) 838-8347.

1981

January 12—**Abdominal Pain.** Seattle. Monday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education and Training Dept., 1551 North 120th, Seattle, WA 98133. (206) 346-0500, Ext. 1737.

January 16-17—**Beta Blocking Agents/Calcium Antagonists.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

January 23—**The Foot.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

January 23-24—**Developmental Disorders in Children.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

January 24—**New Approaches to Gastrointestinal Bleeding.** Tacoma. Saturday. St. Joseph Hospital. Contact: CME Pierce County.

January 26—**Lipids and Diabetes—U/W Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

January 27—**Univ. of Wash. OB/GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

January 29-30—**Financial Planning for Physicians.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

January 31—**The Care of Normal Children.** Seattle. Saturday. Group Health Hospital, 6th Floor Conference Area. Contact: Jackie Kersh, Office of Medical Education, 201 16th Avenue East, A-5, #321, Seattle, WA 98112. (206) 326-7349.

February 5-6—**Schizophrenia and Depression.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

February 6-7—**Workshops in Fluid and Electrolyte Disorders.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

February 10—**Anesthesiology and Pediatrics—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

February 12-14—**National Health Service Corps.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

February 14-21—**Perinatal Critical Care.** Sun Valley, ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Sports Medicine.** Sun Valley, ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Practical Neurology.** Ilikai, Honolulu, Hawaii. Saturday-Saturday. U/W at Ilikai, Honolulu, Hawaii. Contact: U/W School of Medicine.

February 21-28—**Metabolism and Endocrinology.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

February 23—**Emergency Medical Services—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD. P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

February 27—**Diagnosis and Treatment of Common Arthritic Diseases.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 5-6—**Preventing/Surviving Stress as a Physician.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

March 6-7—**Clinical Pharmacology for the Practitioner.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 7—**Handicapped Child.** Seattle. Saturday. Contact: U/W School of Medicine.

March 12-13—**Tacoma Academy of Internal Medicine.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 12-13—**Diabetes in General Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

March 16—**Gyn Oncology—Univ. of Wash. OB/GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 17—**Epilepsy.** Spokane. Tuesday. Contact: U/W School of Medicine.

March 23—**Pain—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 23-27—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

March 26-27—**Sexually Transmitted Diseases.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

March 30-April 10—**Rehabilitation Medicine Review.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

April 3—**Nutrition in the Hospitalized Patient.** Seattle. Friday. Contact: U/W School of Medicine.

April 4—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

April 4-11—**Current Concepts in OB/GYN.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Office Management of Chronic Pain.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Wailea, Maui, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Drug Therapy.** Maui, Hawaii. Saturday-Saturday. U/W at Royal Lahaina, Maui, Hawaii. Contact: U/W School of Medicine.

April 14—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

April 16-18—**Modern Diagnostic Techniques: Use/Abuse.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

April 17-18—**Modern Office Procedures: Minor Surgeries.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

April 18-25—**Emergency Medical Care.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

April 27—**Total Parenteral Nutrition—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 30-May 2—**Trauma.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

May 1—**Management of Acute Medical Problems.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 7-8—**Medical Genetics and Teratology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 15-16—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 15-16—**Medical Alumni.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

May 18—**Arrhythmias—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 19—**Evaluation and Treatment of Premature Labor—Univ. of Wash. OB/GYN Sessions.** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 21-22—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 23-30—**Allergy and Immunology.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

June 4-6—**Radiology Northwest V.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 4-5—**Pacific Northwest Chapter of the American College of Chest Physicians: Cardiopulmonary Symposium.** Seattle. Thursday-Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

June 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

June 11-12—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 15-19—**Death Investigation.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

June 18-19—**Respiratory Care.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 22—**Pulmonary Disease—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

July 25-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Saturday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education,

540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221
SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

November 19
SPONSOR: Cottonwood Hospital
TITLE: **Tumor Conference**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

November 21
SPONSOR: Cottonwood Hospital
TITLE: **Common Dermatological Problems of Children**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

December 2
SPONSOR: Cottonwood Hospital
TITLE: **Post-Myocardial Infarction Rehabilitation**
LOCATION: CWH
FEE: None
CREDIT: 1 hour
CONTACT: Pat Olsen (801) 262-3461

December 10-12
SPONSOR: VeteransAdministration/University of Utah/ American Cancer Society/LDS Hospital
TITLE: **Cancer Update Conference**
LOCATION: Hotel Utah, Salt Lake City
FEE: Non-VA $40.00
CREDIT: 17 hours
CONTACT: Mark W. Wolcott, MD (801) 582-1565

December 12
SPONSOR: LDS Hospital
TITLE: **An Afternoon of Cardiology—Hypertension**
LOCATION: LDSH, 7th Floor Conference Room
FEE: To be announced
CREDIT: To be announced
CONTACT: Stan Everett (801) 350-1004

1981

January 17-21
SPONSOR: Utah Ophthalmological Society/University of Utah/ Johnson & Johnson
TITLE: **Interocular Lens Course**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 24 hours
CONTACT: A. Thomas Williams, MD (801) 262-6111

January 24-31
SPONSOR: University of Utah
TITLE: **6th Annual Snowbird Radiology Conference**
LOCATION: Snowbird
FEE: To be announced
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8188

January 31-February 7
SPONSOR: University of California, San Francisco, CA
TITLE: **Infectious Diseases in Clinical Practice**
LOCATION: Park City
FEE: $200.00 ($250.00 after October 15, 1980)
CREDIT: 20 hours
CONTACT: Extended Programs in Medical Education
University of California
1308 3rd Avenue
San Francisco, CA 94143
(415) 666-2483 or 666-2894

February 9-12
SPONSOR: University of Utah
TITLE: **10th Annual Family Practice Refresher Course**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 28 hours
CONTACT: David N. Sundwall, MD (801) 581-8633

February 15-20
SPONSOR: University of Utah
TITLE: **Update on Clinical Microbiology and Immunology**
LOCATION: Park City
FEE: To be announced
CREDIT: 24 hours
CONTACT: John M. Matsen, MD (801) 581-5514

February 17-20
SPONSOR: Primary Children's Medical Center
TITLE: **Postgraduate Course in Pediatric Surgery**
LOCATION: Park City
FEE: $250.00
CREDIT: 12 hours
CONTACT: Stan Everett (801) 350-1100

February 20-24
SPONSOR: University of Utah
TITLE: **26th Annual Postgrad Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: 16 hours
CONTACT: Theodore H. Stanley, MD (801) 581-6393

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UU: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

February 21-24
SPONSOR: University of Utah
TITLE: **22nd Annual OB-BYN Course**
LOCATION: Holiday Inn, Park City
FEE: $250.00
CREDIT: 15 hours
CONTACT: David H. Engelberg, MD (801) 581-7647

February 22-27
SPONSOR: Utah Ophthalmological Society
TITLE: **OUS Winter Meeting**
LOCATION: Park City
FEE: To be announced
CREDIT: 12 hours
CONTACT: A. Thomas Williams, MD (801) 268-6111

February 25-27
SPONSOR: University of Utah/Intermountain Pediatric Society/ American Academy of Pediatrics
TITLE: **Common Problems in Pediatrics III**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 16 hours
CONTACT: Bruce Buehler, MD (801) 581-7877

February 25-28
SPONSOR: University of Utah
TITLE: **Gynecologic Oncology Course**
LOCATION: To be announced
FEE: To be announced
CREDIT: 15 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-March 7
SPONSOR: University of Utah
TITLE: **Midwinter Radiology Pacific Cruise Meeting**
LOCATION: Departs from Los Angeles
FEE: $300.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

February 28-March 7
SPONSOR: University of Utah
TITLE: **6th Annual Advances in Internal Medicine**
LOCATION: Snowbird
FEE: $225.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

February 28-March 7
SPONSOR: University of Utah
TITLE: **Nutrition and Contemporary Medicine**
LOCATION: Park City
FEE: $200.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 7-14
SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 14-21
SPONSOR: University of Utah
TITLE: **3rd Annual Park City Radiology Conference: Neuroradiology**
LOCATION: Park City
FEE: $240.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

April 8-10
SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ University of Arizona Center for Occupational Safety and Health/University of Texas Health Science Center, School of Public Health
TITLE: **3rd Annual Park City Environmental Health Conference: Legal and Ethical Dilemmas in Occupational Health**
LOCATION: Prospector Square Lodge, Park City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

June 22-25
SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1981—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 22-26, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1981—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1981—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: 1981—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Interim Session: November 14-15, 1980, Kachina Lodge, Taos.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-31, 1980, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: 1981—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: 1981—date and place to be announced.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Ramada Snow King Inn, Jackson.

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Librium® C-IV 5mg, 10mg, 25mg capsules
chlordiazepoxide HCl/Roche

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral–Adults:* Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d.* *Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) *Capsules*, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Libritabs® (chlordiazepoxide) *Tablets*, 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable.

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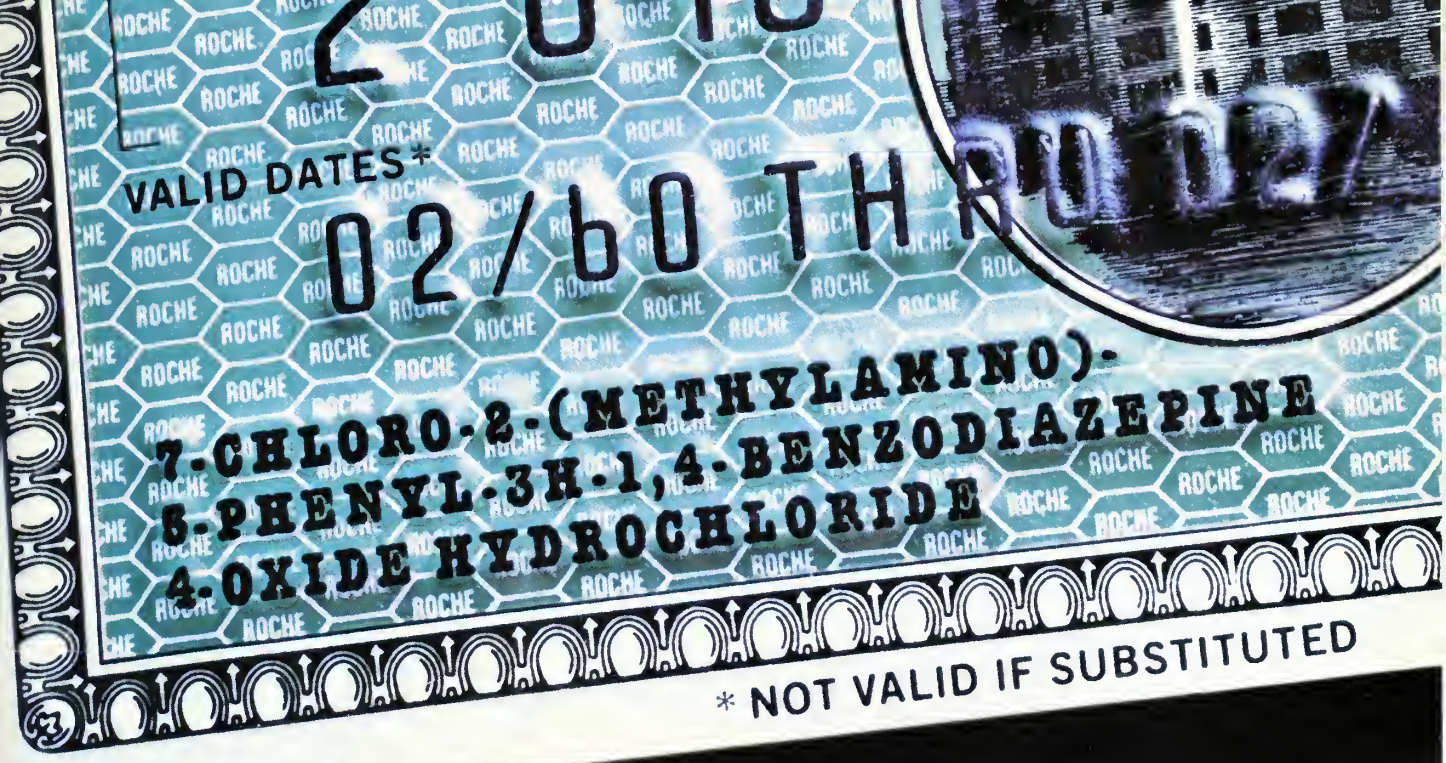

Do you know me?

I'm the first benzodiazepine used clinically
I've been around for 20 years
I have a quarter century of documented efficacy
I have an excellent safety profile
I have a predictable patient response
I have minimal effect on mental acuity; during therapy, however, caution is advised against driving or use of alcohol.

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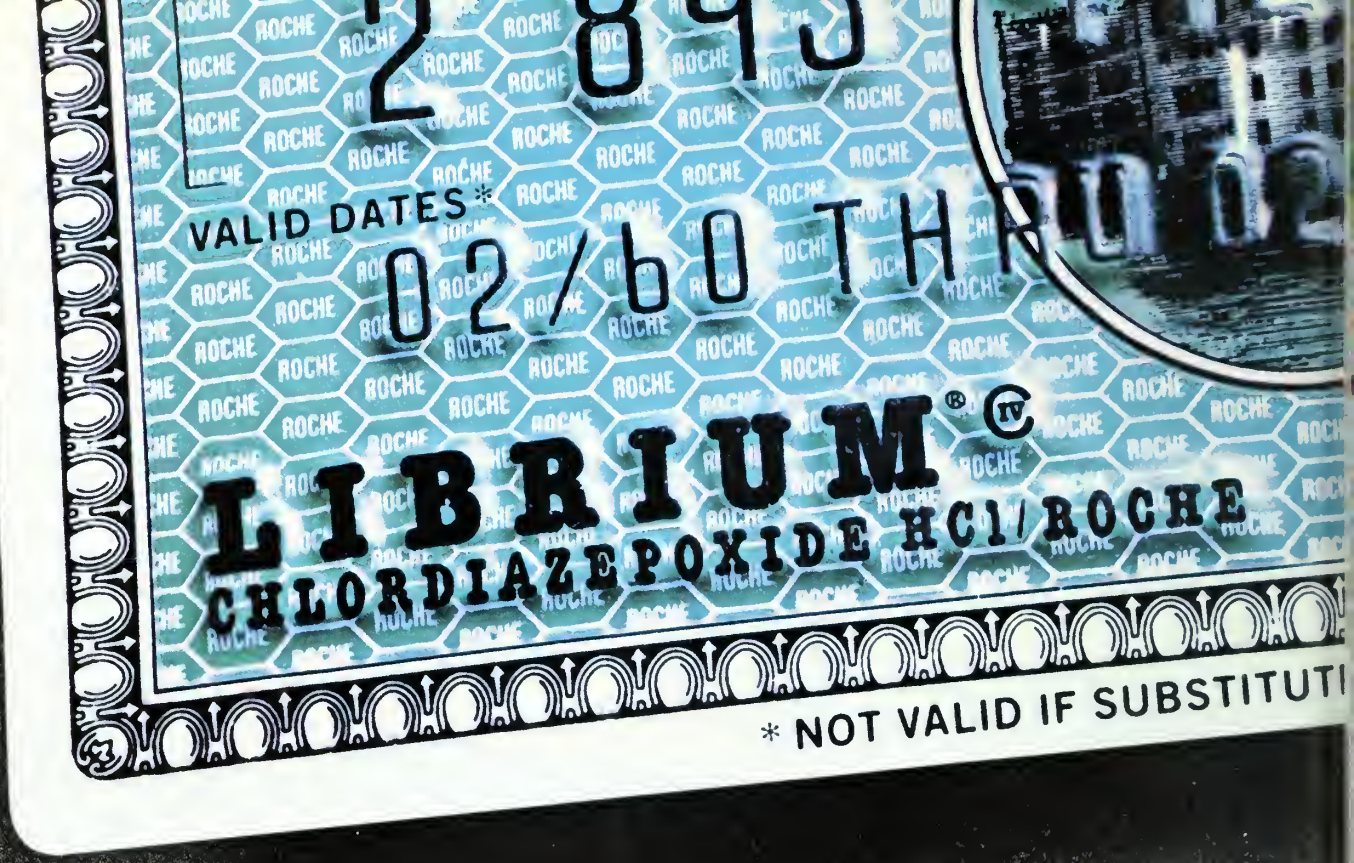

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★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA, MONTANA AND IDAHO; OREGON; WASHINGTON; UTAH (See Advertising Page 27)**

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**

CONSIDER THE COMPARATIVE EFFICACY OF DALMANE® VS. (flurazepam HCl/Roche) OTHER SLEEP MEDICATIONS

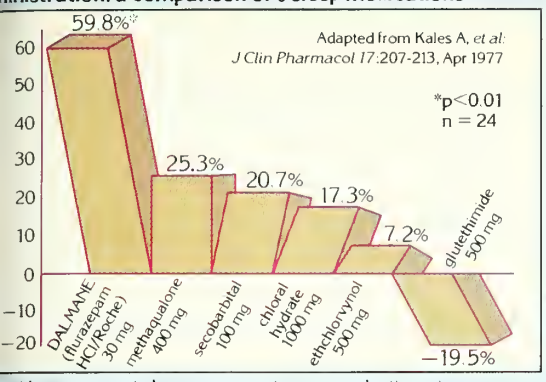
Sleep research laboratory studies show Dalmane (flurazepam HCl/Roche) **more effective for more nights than other sleep medications tested**

Polygraphic appraisal of sleep in 36 insomniac subjects over 14 consecutive nights, proved that of the 9 medications* tested, only Dalmane remained significantly effective for the duration of the study.[1]

While it is reassuring that efficacy can be maintained for this period of time if needed, pharmacological treatment of insomnia should be initiated with the lowest possible effective dose and continued only as long as judged appropriate to achieve a therapeutic goal.

*The drugs studied included 7 commercially available and 2 investigational hypnotics.

cent decrease in total wake time after 12-14 nights of ministration: a comparison of 6 sleep medications.



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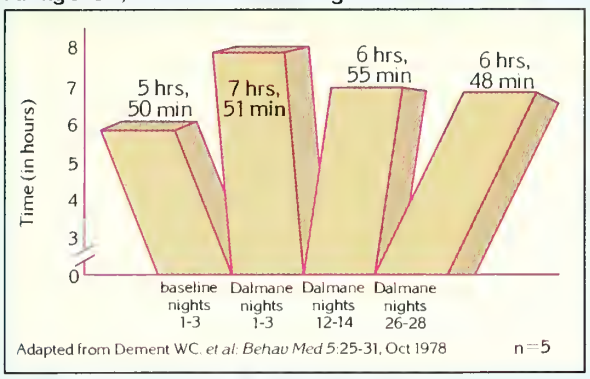
Dalmane (flurazepam HCl/Roche) improved sleep during short, intermediate and longer-term use.



Improvement shown represents mean improvement, in hours, of total sleep time.

ditional studies showed that Dalmane ırazepam HCl/Roche) continued to provide ective insomnia relief for 28 consecutive hts of use

o sleep research laboratory studies with tal of 10 insomniacs investigated for 280 ject nights, conducted at geographically arated university medical centers, proved longer-term usefulness of Dalmane.[2,3] lthough insomnia is often transient, it may netimes be necessary to continue treatment periods up to 4 weeks. If so, careful assess-nt of the patient's medical profile should be de, with special attention to periodic blood ınts and liver and kidney function tests.

Plus, efficacy proved in elderly insomniacs with the 15 mg dosage *h.s.*

Six insomniac patients, aged 67 to 82 years, averaged 1 hour and 23 minutes more sleep nightly during treatment with Dalmane for a period of one week.[4] It should be kept in mind that sleep medication may not always be appropriate for elderly individuals who complain of insomnia. Contributing factors may include requirements for less sleep than in younger years or the establishment of poor sleeping habits, such as napping during the day.

REFERENCES:

1. Kales A, *et al: J Clin Pharmacol 17*:207-213, Apr 1977
2. Dement WC, *et al: Behav Med 5*:25-31, Oct 1978
3. Kales A, *et al: Clin Pharmacol Ther 19*:576-583, May 1976
4. Frost JD Jr, De Lucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979

DALMANE®℠

flurazepam HCl/Roche

15-mg and 30-mg capsules

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PROTOCOL FOR INSOMNIA MANAGEMENT

- ☐ Treat physical and/or psychological factors that may underlie an inability to sleep.
- ☐ Thoroughly question and evaluate new patients who specifically request sleep medications.
- ☐ Consider other medications the patient may be taking (including alcoholic beverages) and be aware of possible drug interactions.
- ☐ Select a sleep medication with objectively documented proof of efficacy and a wide margin of safety.
- ☐ Initiate treatment at the lowest effective dose for the period of time deemed necessary to achieve a reasonable therapeutic goal.
- ☐ Monitor response to therapy and, based upon patient reassessment, determine need for continuing medication on an individual basis.
- ☐ Advise patients who ingest alcoholic beverages or other CNS depressants against doing so while on sleep medication. CNS stimulants such as caffeine should also be discontinued.
- ☐ Caution patients against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle shortly after ingesting the drug. In addition, as with all CNS depressants, patients may have reduced motor performance while on hypnotic therapy and should be advised accordingly.
- ☐ Avoid prescribing for suicidal or dependency-prone individuals whose histories indicate an inability to handle any psychoactive substances including alcohol.

DALMANE® ⓒIV

flurazepam HCl/Roche

One 15-mg capsule *h.s.*—recommended initial dosage for elderly or debilitated patients.
One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, e.g., excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg recommended initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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BOSTON
JUN 9 1981

THE WESTERN JOURNAL OF MEDICINE
INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 731 Market Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format, and to give close attention to syntax, grammar and spelling.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed double-spaced throughout (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 2,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

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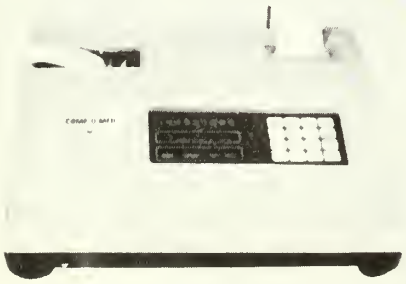

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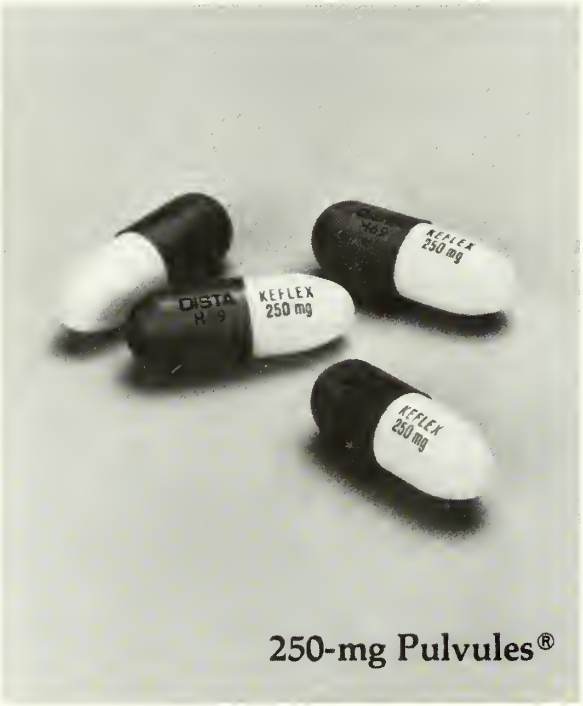

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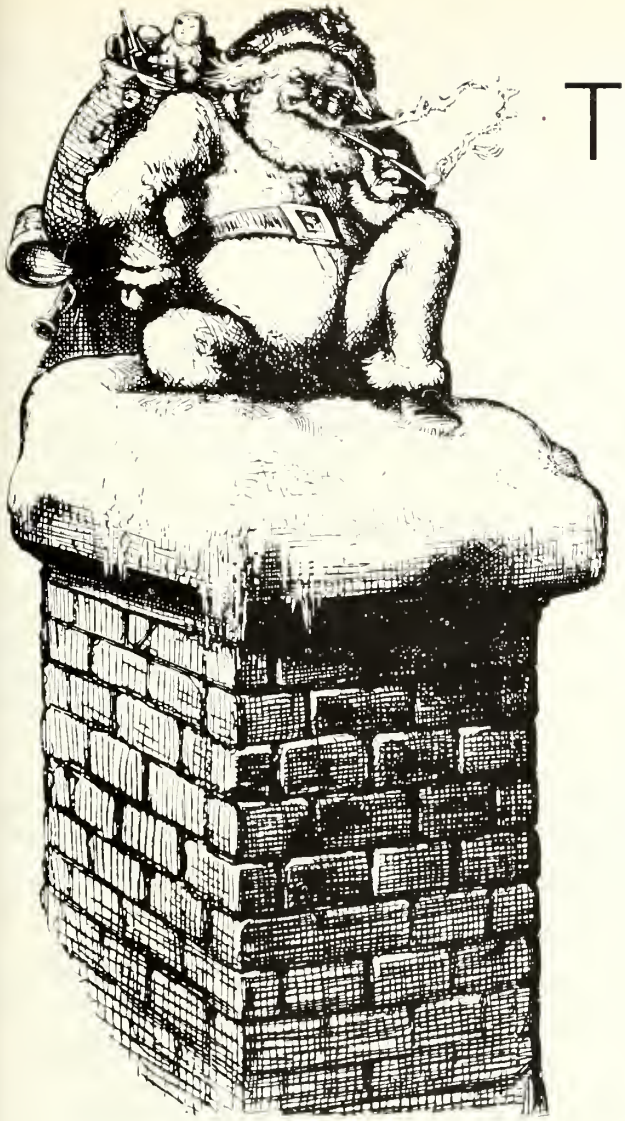

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Deaths From Bites and Stings of Venomous Animals

FRANKLIN ENNIK, MA, *Berkeley, California*

Data abstracted from 34 death certificates indicate that the three venomous animal groups most often responsible for human deaths in California from 1960 through 1976 were Hymenoptera (bees, wasps, ants and the like) (56 percent), snakes (35 percent) and spiders (6 percent). An average incidence of 2.0 deaths per year occurred during these 17 years, or an average death rate of 0.01 per 100,000 population per year. Nearly three times more males than females died of venomous animal bites and stings. Half of the deaths from venomous snake bites occurred in children younger than 5 years of age. Susceptible persons 40 years or older appeared to be particularly vulnerable to hymenopterous insect stings and often quickly died of anaphylaxis. Fatal encounters with venomous animals occurred more often around the home than at places of employment or during recreational activities. Deaths resulting from spider bites are rare in California but many bites are reported. Medical practitioners are urged to seek professional assistance in identifying offending animals causing human discomfort and to use these animals' scientific names on death certificates and in journal articles.

ANIMALS THAT PRODUCE toxins are classified as either venomous or poisonous.[1] Venomous animals are those that are capable of producing a toxin in a specially developed secretory organ or group of cells, and can deliver this toxin during a stinging or biting act via an apparatus, such as stings or spines or by contact hairs, teeth, beaks or fangs. This category includes stone fish, stingrays, snakes, spiders, scorpions, ticks and insects such as Hymenoptera (bees, wasps, ants and the like), caterpillars and conenose bugs. Poisonous animals are those creatures whose tissues, either in whole or in part, are toxic, such as puffer fish, toads and newts.

In an analysis of human deaths attributable to venomous animals that occurred in the United States from 1950 through 1959, Parrish[2] found that hymenopterous insects, snakes and spiders were the three animal groups most often responsible. Since 1963 data have been summarized for Florida,[3] Mississippi,[4] and England and Wales.[5] Parrish[2] included in his report for the United States the deaths in California attributed to bites and stings of venomous animals during 1950 to 1959. This study also summarizes data on human

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deaths resulting from venomous animal bites and stings that occurred in California from 1960 through 1976.

Methods

Copies of death certificates coded under the International Classification of Diseases Adapted (ICDA),[6] "Bites and Stings of Venomous Animals and Insects," for the years 1960 through 1976, were obtained from the Vital Statistics Section of the California State Department of Health Services. The ICDA codes E927 (7th edition, 1957) and E905 (8th edition, 1967) include fatalities resulting from bites or stings of venomous sea animals, venomous lizards and snakes, centipedes, spiders, scorpions, bees, wasps and unspecified insects. Excluded are fatalities caused by nonvenomous animals such as dogs, cats, farm animals, birds, nonvenomous snakes (constrictors) and nonvenomous insects. The following information was abstracted and summarized from the death certificates: the age, sex and occupation of the deceased; the town and county where the accident occurred; the date, time, place and cause of death; the animal presumed to have been the cause of death, and the time between the injury and death.

TABLE 1.—*Deaths and Venomous Animals Responsible for Fatalities in California, 1960-1976, Compared With 1950-1959**

	*1950-1959**		*1960-1976*	
Animal	*Number of Deaths*	*Percent*	*Number of Deaths*	*Percent*
Hymenoptera	18	56	19	56
Venomous snakes	12	38	12	35
Spiders	1	3	2	6
Unspecified insect	..	..	1	3
Other	1	3	..	..
TOTAL	32	100	34	100

*Data adapted from Parrish.[2]

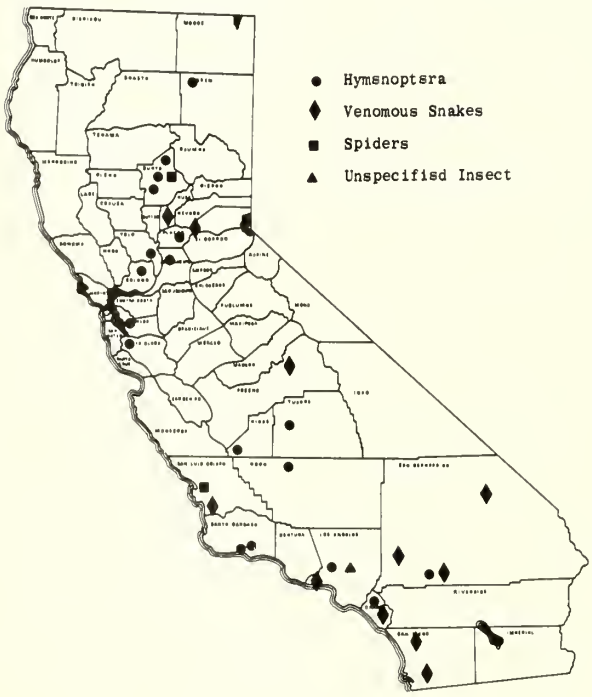

Figure 1.—Locations where bites and stings occurred that resulted in human deaths. Each symbol represents one death. Two deaths of California residents that occurred out-of-state are not indicated.

Results and Discussion

Parrish[2] reported 32 human deaths attributed to bites and stings of venomous animals in California from 1950 through 1959, or an average incidence of 3.2 deaths per year. The results of the present study indicate that 34 deaths occurred as a result of venomous animals from 1960 through 1976 (Table 1). This represents an average of 2.0 deaths per year for this 17-year period and an average death rate of 0.01 per 100,000 population per year (range 0 to 0.036).

In this study, the numbers of deaths categorized by cause (Table 1) are similar to those reported by Parrish.[2] Nineteen deaths (56 percent) were caused by hymenopterous insects: bees (14), wasps (4), and yellowjackets (1). Twelve deaths (35 percent) were caused by venomous snakes: rattlesnake (8), king cobra (1) and "poisonous snake" (3). Two deaths (6 percent) were attributed to spiders and one (3 percent) to an unspecified insect. No deaths attributed to other venomous animals such as marine animals, ants, caterpillars, centipedes, scorpions, ticks and poisonous lizards, were reported in California during this period.

Figure 1 illustrates the localities in California where the fatal bites or stings occurred. Obvious concentrations appear in the distribution of deaths. The concentration of fatalities from hymenopterous insect stings in the Sacramento Valley and lower San Joaquin Valley correlates with the large number of bee colonies commercially kept in these areas for agricultural purposes. However, there is no direct evidence that the commercially kept bees are responsible for these deaths. Although beekeeping was not listed as an occupation of any person in this study, most deaths due to Hymenoptera stings occurred "at

home." Because honey bees are necessary for the economic well-being of these farming communities their presence may be tolerated in the adjacent suburban areas as well, even though the bees are a potential health threat.

The concentration of deaths from snakebites in Southern California may be due, in part, to the large number of rattlesnake species that occur in the diverse habitats of that region. In addition, the daily and seasonal activity periods of rattlesnakes in this area may be prolonged compared with other regions, which may permit more frequent accidental contact with humans. Also, many species of exotic and indigenous venomous snakes are housed in private and scientific collections in Southern California.[7]

There were nearly three times more deaths among males than females between 1960 and 1976 (Table 2). This difference possibly reflects the greater exposure of males to venomous animals because they spend more time in outdoor activities. However, the number of fatalities among men and women may equalize in the future because of changes in women's occupational and recreational patterns.

Nearly all age groups are represented in the distribution of victims (Table 3). Half of the recorded fatalities due to snakebites occurred among children younger than 5 years of age. Children appear to be particularly vulnerable to snakebites not only because of their small size and curiosity, but also because most young children have not yet learned to recognize venomous snakes or to give them the respect they deserve.

Sixteen deaths or 84 percent of the recorded fatalities due to Hymenoptera stings occurred in persons 40 years of age or older. People younger than 40 years apparently are less susceptible to fatal stings of Hymenoptera because hypersensitivity to the venom has not yet developed. Somerville and co-workers[5] observed a substantial increase in the number of fatalities among persons older than 40 years in their study of 61 deaths caused by Hymenoptera stings in England and Wales.

Table 4 lists the times of day when the injuries (envenomations) occurred and the approximate interval from envenomation until death for each victim. For the most part, fatal Hymenoptera stings occurred during daylight hours, reflecting the insects' period of greatest activity and potential contact with humans. Apparently, most victims were unable to obtain medical help in time and died within an hour, in most cases (14 of 19) because of anaphylactic shock. Most deaths caused by Hymenoptera were attributed to a single "sting," although two death certificates indicated that the persons had died from "multiple" stings.

Some allergists[8,9] believe that about 1 percent of the general population is hypersensitive to Hymenoptera venom. This means that up to some 2 million people in the United States or about 220,000 in California could be hypersensitive to these toxins.

Bites from venomous snakes occurred most frequently in the afternoon and early evening hours. With the exception of small children, who succumbed soon after envenomation, the victims

TABLE 2—*Deaths by Year and Sex of Victims of Bites and Stings in California, 1960-1976*

Year	*Females*	*Males*	*Deaths*
1960	..	..	..
1961	1	1	2
1962	..	2	2
1963	..	1	1
1964	1	..	1
1965	..	..	..
1966	..	4	4
1967	2	5	7
1968	..	3	3
1969	..	..	..
1970	1	..	1
1971	1	2	3
1972	..	..	..
1973	..	3	3
1974	..	3	3
1975	..	1	1
1976	1	2	3
TOTAL	7	27	34

TABLE 3.—*Age Distribution of Victims Who Died From Bites and Stings of Venomous Animals in California, 1960-1976*

Age of Victim (Years)	*Venomous Snake Bites*	*Hymenoptera Stings*	*Spider Bites*	*Unspecified Insect Bite*	*Deaths*
0-4	6	..	..	..	6
5-9	..	..	..	..	..
10-19	..	2	..	1	3
20-29	2	1	..	..	3
30-39	1	..	..	..	1
40-49	1	5	2	..	8
50-59	..	5	..	..	5
60-69	..	6	..	..	6
70 & older	2	..	..	..	2
TOTALS	12	19	2	1	34

survived several hours to several days after being bitten. Because the venom is absorbed primarily through the lymphatic system and to a lesser degree directly into capillaries, there is a delay of some hours before the toxin affects vital organs. The only death between 1960 and 1976 attributed to a venomous animal not native to California occurred when a professional snake handler was bitten while attempting to force-feed a king cobra.

Deaths resulting from spider bites are rare in California. However, the number of people bitten per year is greater than is generally realized. Statistical data maintained at two regional poison centers (A. S. Manoguerra, PharmD, University of California, San Diego, written communication, August 1979, and S. Stowe, RN, University of California, Davis, written communication, April 1979) show approximately 100 calls per year at each center regarding spider bites. The Vector Biology and Control Section of the California Department of Health Services responds to between 45 and 75 inquiries per year on real and suspected spider bites. Russell[10] stated that he saw 27 victims of black widow bite over three years in the greater Los Angeles area. One death certificate in the present study alleged that the ". . . deceased [was] bitten on [the] neck by an insect [sic], presumed to have been a black widow. . . ." The bite later had become infected. The other death certificate examined, which attributed death to a spider bite, alleged that the victim was ". . . apparently bitten by a spider. . . ." Medical entomologists of the California Department of Health Services investigated the latter case but failed to find evidence indicating the presence of either black widow spiders (*Latrodectus* sp) or violin spiders (*Loxosceles* sp) in the locale where the victim had been reported bitten. These two genera are usually implicated in human deaths from spider bites. *Latrodectus* spiders are found throughout California, mainly at lower elevations. One or more indigenous species of *Loxosceles*

TABLE 4.—*Injury and "Immediate Cause" of Death in Victims of Stings and Bites of Venomous Animals in California, 1960-76*

Injury	*Approximate Time of Day (Pacific Standard Time)*	*Approximate Interval to Death*	*"Immediate Cause" (According to Death Certificate)*
Bee sting	0600	½ hour	Anaphylactic shock
Bee stings	0800	½ hour	Acute pulmonary edema
Bee sting	0915	2 hours	Anaphylaxis
Bee sting	1000	Not stated	Acute asthmatic bronchitis
Bee sting	1150	1 hour	Anaphylaxis
Bee sting	1300	<½ hour	Anaphylactic shock
Bee sting	1300	½ hour	Anaphylactic shock
Bee sting	1430	<1 hour	Asphyxia
Bee sting	1725	½ hour	Intoxication due to bee sting
Bee sting	1800	¾ hours	Anaphylaxis
Bee sting	1800	½ hour	Anaphylactic shock
Bee sting	1800	2 hours	Anaphylactic reaction
Bee sting	2130	8 hours	Anaphylaxis
Bee sting	Unknown	Unknown	Anaphylactic shock
Wasp sting	0730	<1½ hours	Anaphylactic shock
Wasp sting	1030	1 hour	Anaphylactic shock
Wasp sting	1500	1½ hours	Passive congestion of heart
Wasp sting	1800	4 hours	Anaphylaxis
Yellowjacket stings	Unknown	2 days	Coronary occlusion—shock
Rattlesnake bite	0900	1 day	Not stated
Rattlesnake bite	1100	3 hours	Not stated
Rattlesnake bite	1400	18 hours	Hemolysis
Rattlesnake bite	1430	4½ days	Cardiorespiratory failure
Rattlesnake bite	1500	14 hours	Respiratory paralysis—toxemia
Rattlesnake bite	1900	7 hours	Acute pulmonary congestion
Rattlesnake bite	1900	<1 day	Not stated
Rattlesnake bite	Unknown	<½ hour	Hemolysis
King cobra bite	1800	<½ hour	Pulmonary emphysema atrophy
Snake bite	1315	4 hours	Acute toxemia
Snake bite	1800	Unknown	Cardiorespiratory failure
Snake bite	1815	3½ days	Cardiorespiratory failure
Black widow spider bite	Unknown	8½ days	Myocarditis and pericarditis
Spider bite	Unknown	9½ days	Cardiac arrest (septicemia)
Insect bite	Unknown	7 days	Septicemia from cutaneous abscess

spiders occur in the desert habitats of Southern California and at least one exotic *Loxosceles* species has become established in the San Gabriel Valley area of Los Angeles County.[11] Parrish[2] reported two deaths caused by *Loxosceles* spiders and 63 deaths attributed to bites by *Latrodectus* spiders in the United States between 1950 and 1959.

The seasonal distribution of deaths caused by venomous animals is summarized in Table 5. Although accidental encounters with venomous snakes can occur at any time in certain geographic areas, humans are at particular risk of being bitten by these animals beginning in April in some western states. Rattlesnakes begin to emerge from their sites of winter hibernation to forage or bask in the sun at this time or at other times when ambient air temperatures increase. Although some species of rattlesnake appear to be sluggish or less pugnacious than others, all should be considered dangerous during any season of the year.

The seasonal pattern of human fatalities from Hymenoptera stings corresponds to the seasonal increase and decrease of the foraging insect populations. In the spring when the weather becomes favorable, humans and Hymenoptera increase their outdoor activities. Close encounters often result in stings that are sometimes fatal. The occurrence of fatal stings reaches a peak in late summer and abruptly decreases when winter weather approaches.

The use of data from death certificates to determine the incidence of deaths from venomous animals leads to an underestimation of the actual number because of misdiagnoses. Many fatalities that have occurred outdoors, which were classified as heat strokes or heart attacks, might actually have been allergic reactions to insect stings.[12] Also, examining physicians may not have recognized insect stings as a cause of death, especially when an accident with an automobile[13] or equipment was involved. Two death certificates examined during this study indicated that the victims had suffered fatal Hymenoptera stings while operating motor vehicles. Additional deaths attributable to insect stings might have been recorded under other ICDA codes or classifications.

Although the number of death certificates examined during this study was small, the data suggest certain trends. Fatal encounters with venomous animals occurred more often at home than at work or during recreational activities (Table 6). This was particularly true for cases of Hymenoptera stings. Bee stings and yellowjacket stings appear to occur more often in suburban environments than in rural or farming areas. These particular insects are often tolerated as beneficial animals, even though they are potentially life threatening. In contrast, venomous snakes are not tolerated in or near suburban areas and seem to be the most prevalent cause of fatalities in rural or wild areas.

Equal numbers of deaths attributed to bites and stings of venomous animals were reported from January 1960 through June 1968 as from July 1968 through December 1976. In the first period 10 deaths resulted from snake bites while in the second period they were responsible for only 2 of 17 deaths. In contrast, only 6 of 17 deaths in the first period were due to Hymenoptera stings, but 13 deaths were caused by these insects in the second period. A general migration toward new suburban developments by city dwellers not familiar with the hazards of the countryside may explain some of the fatalities during the latter period.

Often, the animals responsible for the fatalities are indicated on death certificates by their common or vernacular names. For example, the name wasp is a broad term that includes yellowjackets

TABLE 5.—*Human Deaths Attributed to Bites and Stings of Venomous Animals by Month in California, 1960-1976*

Month	*Venomous Snake Bites*	*Hymenoptera Stings*	*Spider Bites*	*Unspecified Insect Bite*	*Deaths*
Jan	..	..	..	..	..
Feb	..	..	..	..	..
Mar	..	..	..	..	..
Apr	3	..	..	..	3
May	2	1	..	..	3
Jun	1	2	..	..	3
Jul	4	3	1	..	8
Aug	..	..	..	1	1
Sep	..	6	..	..	6
Oct	1	5	..	..	6
Nov	..	1	1	..	2
Dec	1	1	..	..	2
TOTALS	12	19	2	1	34

TABLE 6.—*Place Where Fatal Encounters With Venomous Animals Occurred*

Animal	*Home*	*Work*	*Recreation*	*Unstated*	*Total*
Hymenoptera	9	5	2	3	19
Venomous snakes	4	2	6	..	12
Spiders	1	..	..	1	2
Unspecified insect	..	..	1	..	1
TOTALS	14	7	9	4	34

and hornets among others. Bee is a similar broad term which includes honey bees among others. The accuracy of using such terms as spider, wasp, bee, honey bee, yellowjacket, hornet and, perhaps, rattlesnake on death certificates *and* in medical literature for descriptive purposes is open to question. These terms, often in combination with various colors, are not descriptive in any scientific sense when used without also giving the animal's scientific name. Furthermore, these common names, as used by the lay public and in medical literature, often refer to different genera and species in various geographic regions of the country.

Animal venoms differ remarkably in their composition and modes of action. The following examples illustrate the importance of specificity in the identification of the offending animals. Recent studies on Hymenoptera venom suggest that the venom components of some vespid genera are qualitatively, but not necessarily quantitatively, similar for phylogenetically related species.[14] Similarly, the effects of venom on humans of the many species in the scorpion genus *Centruroides* in the United States vary, according to species, from transient local pain to serious neurological effects. It is likely that the numerous reports of necrotic arachnidism now being attributed to the spider genus *Loxosceles,* particularly in locales where they are not endemic or not likely to be found, will be traceable to other species of spiders.[15] Unfortunately, physicians often have to rely on descriptions by their patients, who did not capture the arthropods.

As an entomologist and a biologist, I urge medical practitioners to seek professional assistance in identifying the genus or species name of animals that have caused discomfort or illness in their patients and to use these names in scientific reporting and on death certificates. Whenever possible, patients or friends should be urged to capture (taking precautions to avoid exposure) and submit the offending animal for identification.

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Therapy of Anorectal Gonorrhea in Men

Efficacy of Oral Antibiotic Regimens

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The results of therapy in 916 men with anorectal gonorrhea treated with orally given antibiotic drugs were reviewed retrospectively. There was a 17.8 percent failure rate for tetracycline (total dose, 10 grams) and a 10.7 percent failure for 3.5 grams of ampicillin plus 1 gram of probenicid. Repeating the ampicillin plus probenicid dose once in 8 to 14 hours reduced the failure rate to 1.6 percent, an efficacy comparable to the regimen of 4.8 million units of aqueous procaine penicillin G given intramuscularly plus 1 gram of probenicid given orally for treatment of anorectal gonorrhea.

THERE ARE FEW DATA in the medical literature evaluating the efficacy of regimens of orally given antibiotic drugs recommended by the United States Public Health Service (USPHS)[1] for the treatment of anorectal gonorrhea in men. In a previous retrospective study one of us (M.S.) reviewed the results of therapy for 606 men with culture-documented anorectal gonorrhea seen at a San Francisco venereal diseases clinic.[2] In that study, of the 451 patients given 4.8 million units of aqueous procaine penicillin G (APPG) intramuscularly plus 1 gram of probenicid orally, the treatment failure rate was 3.3 percent. In 97 patients treated with 2 grams per day of tetracycline hydrochloride given orally in divided doses for five days and in 27 patients given 3.5 grams of ampicillin trihydrate plus 1 gram of probenicid orally according to USPHS recommendations, the treatment failure rates were 14.4 percent and 14.8 percent, respectively. This study evaluates the results of therapy in 916 men treated with orally given antibiotic drugs for anorectal gonorrhea.

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Patients and Methods

In July 1979 the San Francisco City Venereal Diseases Clinic experienced a supply shortage of aqueous procaine penicillin G. During this time a two-dose regimen of ampicillin plus probenicid was administered. The first dose, consisting of 3.5 grams of ampicillin trihydrate plus 1 gram of probenicid, was given orally at once; the same dose was repeated 8 to 14 hours later. This regimen was evaluated in an open, nonrandomized trial for treatment of anorectal gonorrhea in men. The results of this initial trial and subsequent cases treated with this regimen are discussed below.

An extensive search of the clinic files identified the cases of 916 men seen between January 1, 1978, and December 31, 1979, who had received an oral antibiotic regimen for the treatment of anorectal gonorrhea. Cases were identified solely on the basis of a positive rectal culture for gonorrhea. In each case included in this study a follow-up rectal specimen was obtained for culturing 3 to

TABLE 1.—*Results of Oral Antibiotic Therapy for 916 Men With Anorectal Gonorrhea*

	Number of Patients (N=916)	*Number of Treatment Failures*	*Failure Rate (percent)*
Tetracycline hydrochloride	337	60	17.8
Single-dose ampicillin plus probenicid	271	29	10.7
Two-dose ampicillin plus probenicid	308	5	1.6

14 days following completion of therapy. Any patient in the study for whom treatment failed was questioned specifically by the examining physician to exclude cases of reexposure.

During the course of the study routine anoscopy was not done, so there is no way to correlate therapeutic results with physical findings. Culturing of rectal specimens was done routinely to screen for asymptomatic gonorrhea in gay (homosexual) men. Approximately two thirds of the cases of rectal gonorrhea found were asymptomatic.

Rectal cultures were done by blind cotton swab in the recommended manner[3] and plated immediately on modified Thayer-Martin media. Cultures were incubated in candle jars within ten minutes of plating. Gonorrhea isolates were identified by oxidase reaction, Gram stain, colony morphology and sugar fermentation testing.

Routine antibiotic sensitivities and penicillinase testing were not carried out. However, no outbreaks of penicillinase-producing *Neisseria gonorrhoeae* were noted during the study period.

Treatments

The three oral antibiotic regimens used during the study period were: 2 grams per day of tetracycline hydrochloride given orally in divided doses for five days (total dose, 10 grams); 3.5 grams of ampicillin trihydrate plus 1 gram of probenicid given as a single total dose; and 3.5 grams of ampicillin plus 1 gram of probenicid given orally at once and then repeated in toto 8 to 14 hours later—this is referred to as the two-dose regimen.

Results

The results are tabulated in Table 1. There were 60 treatment failures (17.8 percent) in 337 patients given the tetracycline regimen. In 37 of the 60 patients, retreatment could be evaluated by follow-up culture. Of these, 32 were cured by intramuscular administration of 2 grams of spectinomycin hydrochloride; 3 with 4.8 million units of aqueous procaine penicillin G given intramuscularly plus 1 gram of probenicid given orally, and 2 with the two-dose orally given regimen of ampicillin plus probenicid. There were no retreatment failures among those available for follow-up.

The single-dose ampicillin (3.5 grams) plus probenicid (1 gram) regimen was given to 271 patients, with treatment failures occurring in 29 (10.7 percent). Of the 29 cases, 20 were followed after retreatment: 12 were cured with intramuscularly given aqueous procaine penicillin G plus probenicid; 1 was cured with the two-dose ampicillin plus probenicid regimen, and 2 were cured with 2 grams of spectinomycin given intramuscularly. Five patients for whom treatment failed were retreated with tetracycline. Of these, two retreatment failures occurred, but the two patients were lost to follow-up.

The initial trial of the two-dose ampicillin plus probenicid regimen included 61 patients. Of this group, 8 were lost to follow-up, 52 were cured and in 1 patient the treatment failed. All 53 patients found this regimen acceptable in spite of minimal gastrointestinal upset that occurred in three. Subsequently, this regimen was adopted by the clinic as an alternate therapeutic choice to APPG plus probenicid for treatment of anorectal gonorrhea. In evaluating a total of 308 patients (including the initial trial group) given this regimen between July 1, 1979, and December 3, 1979, 5 had treatment failures (1.6 percent). Three of these patients were retreated and cured with APPG given intramuscularly plus probenicid, the other two were lost to follow-up.

Comments

This paper is a retrospective review of results of oral antibiotic therapy of 916 men with anorectal gonorrhea. The only other data on these regimens are contained in reviews by Washington[4] on the unpublished results of a study by Zaidi and Reynolds and in a recent paper by Lebedeff and Hochman.[5] Zaidi and Reynolds found 19.4 percent failure in 62 men treated with the single-dose ampicillin plus probenicid regimen and 28.6 percent failure in 39 men treated with tetracycline. Lebedeff and Hochman reported treatment failures in 5.4 percent of 104 men treated with ampicillin plus probenicid and in 18.1 percent of 83 patients treated with tetracycline. In our study, tetracycline was found to have a 17.8 percent

failure rate in 337 men and a 10.7 percent failure rate in 271 men given the single-dose ampicillin plus probenicid regimen. In view of the higher failure rates noted in both Zaidi's group and in our group given a single-dose of ampicillin plus probenicid, Lebedeff and Hochman's results must be questioned.

Tetracycline has been shown to have a high failure rate in all three series. The reasons for this are uncertain. Tetracycline therapy involves a multidose regimen and therapeutic success must depend on continued patient compliance. Increased tetracycline resistance is possible, although there has been no noticeable increase in tetracycline treatment failures for urethral gonorrhea. Perhaps the regimen is inadequate either in dosage or duration or in antibiotic levels achieved locally in the rectal mucosal tissue. Thus, neither of the two oral regimens (the tetracycline or the single-dose ampicillin plus probenicid) appears entirely satisfactory for treatment of anorectal gonorrhea in men.

While APPG plus probenicid remains the recommended therapy for anorectal gonorrhea in men who are not allergic to penicillin, the two-dose oral regimen of ampicillin plus probenicid appears to be a suitable alternative. Failure rate was only 1.6 percent in 308 patients compared with a 3.3 percent failure rate reported previously in 451 patients treated with APPG plus probenicid.[2] This regimen has the further advantages of being given orally in two simple doses and of avoiding the potential procaine reactions associated with APPG. For clinics with a large patient population, it is less expensive per treatment course than APPG and saves nursing time. Further study of the two-dose ampicillin plus probenicid regimen is needed to evaluate its effectiveness against pharyngeal gonorrhea and to determine whether this regimen would be an acceptable alternative to APPG for all cases of uncomplicated gonorrhea in gay men.

Because of the high cost of spectinomycin and its lack of spirocheticidal activity (that is, spectinomycin will not abort incubating syphilis), tetracycline remains the drug of choice in patients who are allergic to penicillin. However, in view of the high failure rate of tetracycline, it is important to follow up patients with culturing of rectal specimens to assure the success of treatment.

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Absence of Nafcillin-Associated Nephritis

A Prospective Analysis of 210 Patients

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In a prospective study of 210 consecutively seen patients receiving nafcillin, no patient's therapy was discontinued because of clinically manifested or suspected nephritis. Administration of nafcillin was discontinued because of an adverse reaction in only two patients, one with a rash and one with neutropenia. In seven of the ten patients in whom renal dysfunction developed during treatment, renal function improved while the patients continued to receive nafcillin. In the remaining three patients, renal failure was attributed to other factors including rhabdomyolysis and myoglobinuria, gastrointestinal hemorrhage and hypotension, and what appeared to be aminoglycoside toxicity.

No renal biopsy studies were done because none were clinically indicated. Although the results of this study do not rule out the possibility that nafcillin may induce nephritis, if it does occur it appears in such a mild form—manifested solely as urinary sediment abnormalities—or so infrequently that it was not detected in this group of patients.

In four patients, leukopenia could not be explained on any basis other than nafcillin administration.

INTERSTITIAL NEPHRITIS is a recognized complication of therapy with many drugs, including several antibiotics, most notably methicillin.[1-6] In 1968, Baldwin and co-workers[1] detected antigen-antibody complexes along the basement membrane of glomeruli and tubules in the kidneys of patients with methicillin-induced nephritis. This histological finding has also been reported by Galpin and colleagues,[7] but was not found in all patients in their series.

The incidence of this complication has been reported to be as high as 33 percent when the drug has been administered for ten days or longer and at least 15 percent in all patients.[4] The development of the reaction has ranged from two days to a month or more after initiation of therapy.[5] In our experience, nephritis is usually reversible and stops when methicillin treatment is

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discontinued. However, for several patients, the reaction resulted in a prolonged hospital stay and increased costs. Irreversible renal dysfunction has been reported as a result of methicillin-associated nephritis.[2-5]

Only two cases of nephritis attributed to nafcillin have been published.[8,9] An additional case confirmed by biopsy specimen has been described in the preliminary results of a cooperative study on staphylococcal endocarditis (M. A. Sande, MD, Chief of Medicine, San Francisco General Hospital, oral communication, March 1980). Two recent reports suggest that nafcillin is less toxic than methicillin. However, only 29 patients in the one series[10] and 22 patients in the other[11] received either methicillin or nafcillin.[9]

We describe our experience with 210 consecutive patients who were treated with nafcillin and monitored prospectively for toxicity.

Patients and Methods

In August 1977, methicillin was deleted from the University of California, San Francisco, (UCSF) Hospital Formulary and replaced by nafcillin. Every patient who received nafcillin during the subsequent seven months was monitored prospectively during therapy for signs and symptoms, as well as for abnormalities confirmed by laboratory tests that were suggestive of interstitial nephritis and other drug-induced reactions.

No attempt was made to interfere with the patients' care and consultation was not offered.

The following information was collected for each patient: age, sex, weight, diagnosis, temperature and blood pressure. Laboratory data included complete blood count (CBC) with differential cell count, blood urea nitrogen, serum creatinine, analysis of urine and liver function tests. These tests were not done on a protocol basis but were carried out only as clinically indicated in the judgment of the physician caring for the patient. The daily dosages of potentially nephrotoxic drugs, the presence of rash and the reasons for discontinuation of nafcillin other than completion of therapy were recorded.

The following definitions were used in evaluating the records of all patients: leukocyturia or hematuria, more than five cells per high power field; proteinuria, 2+ quantity or greater; eosinophilia, more than 5 percent of the total peripheral leukocyte count; fever, new temperature 38°C (100.5°F) or higher, and presence of azotemia, increase of serum creatinine by 0.5 mg per dl or more from baseline values.

At the end of the study period the data were transferred onto keypunch cards, entered into a computer and analyzed by using an SPSS (Statistical Package for the Social Sciences) program.[12] The analysis was keyed to focus on the seven signs and symptoms usually associated with interstitial nephritis: fever, rash, eosinophilia, proteinuria, hematuria, leukocyturia and a decline in renal function.

Urinary eosinophil counts were not obtained. The diagnosis of interstitial nephritis was based on the presence of renal dysfunction associated with two or more of the signs or symptoms listed above, especially fever, eosinophilia and leukocyturia. Because the onset of interstitial nephritis caused by methicillin has been reported to occur as soon as two days after initiation of therapy, all 210 patients were evaluated. However, only those patients who received the drug for six days or longer were included in the statistical evaluation.

No attempt was made to evaluate phlebitis in patients included in this study.

Results

Data were collected on the treatment of a total of 210 patients, ranging in age from newborn to 98 years, with a mean of 33.8 years. There were 112 males (53 percent) and 98 females (47 percent). The duration of therapy ranged from 1 to 44 days (mean 5.7 days). A total of 136 patients (65 percent) received nafcillin for five days or less, 46 patients (22 percent) for six to ten days and 28 patients (13 percent) for more than ten days. The 57 pediatric patients 10 years of age or younger received an average daily dose of 118.5 mg per kg of body weight, with a range of 40 to 225 mg per kg of body weight per day. The 153 patients older than 10 years of age received an average daily dose of 6.4 grams, with a range of 4 to 15 grams a day. A large number of pediatric patients received the drug as a short course (48-hour) perioperative prophylaxis. A total of 158 patients (75 percent) received nafcillin for documented or suspected infection and 52 (25 percent) for perioperative prophylaxis. Of the 74 patients who received nafcillin for six days or longer, 67 (91 percent) were being treated for staphylococcal infection or for infection by staphylococcus and other organisms. The diagnoses in the 67 patients were: bacteremia, 23 (35 percent); pneumonia, 20 (30 percent); endocarditis, 11

(16 percent); infection of the central nervous system, 11 (16 percent), and osteomyelitis, 2 (3 percent).

Patients who received other known nephrotoxic drugs are listed in Table 1. A total of 147 patients (70.0 percent) received either another penicillin, a cephalosporin, an aminoglycoside, another nephrotoxic antibiotic agent (such as vancomycin or tetracycline) or a combination of two or more of these drugs.

A total of 165 patients had 176 episodes of the signs or symptoms usually associated with nephritis (Table 2). Of the 165 patients, 13 had two or more of the signs or symptoms described in Table 2.

TABLE 1.—*Patients Receiving Concomitant Nephrotoxic Drugs*

Drug or Combination	*No. of Patients*
Penicillin	63
Cephalosporin	1
Aminoglycoside	34
Other*	6
Penicillin and cephalosporin	2
Penicillin and aminoglycoside	28
Penicillin and other	1
Cephalosporin and aminoglycoside	3
Aminoglycoside and other	6
Penicillin, cephalosporin and aminoglycoside	2
Penicillin, cephalosporin, aminoglycoside and other	1
TOTAL	147

*Such as vancomycin or tetracycline.

TABLE 2.—*Occurrence of Signs and Symptoms Usually Associated with Nephritis in 165 Patients Treated With Nafcillin*

Signs and Symptoms	*Number of Patient-Episodes**
Fever†‡	14
Rash‡§	8
Eosinophilia†‡§	22
Proteinuria	42
Leukocyturia	53
Hematuria	27
Azotemia‖	10
TOTAL	176

*A total of 176 episodes occurred in 165 patients. The other 45 of the 210 patients in the study had none of the above signs or symptoms.

†Three patients had fever and eosinophilia.

‡One patient had fever, rash and eosinophilia.

§Two patients had rash and eosinophilia.

‖Of the ten patients with azotemia, two also had proteinuria, one also had leukocyturia, one also had proteinuria and leukocyturia, and three had proteinuria, leukocyturia and hematuria.

Table 3 gives the probable causes of fever in 14 patients who became febrile during their course of nafcillin therapy. In none of these patients was therapy discontinued because of suspicion of nephritis, and nephritis developed in none.

A rash developed in eight patients during treatment. In four the rash developed after several days of nafcillin therapy; but no patient had urinary sediments suggestive of nephritis. Thus, therapy was continued in these four and the rashes disappeared. Of the remaining four patients, one was thought to have an incidental contact dermatitis; and in another the rash was attributed to disseminated varicella-zoster infection. In the remaining two patients, rash developed after 24 to 48 hours of therapy; nafcillin was discontinued in one, and in both, the rash disappeared.

Analysis of urine was not done for 57 of the 210 patients while they were undergoing therapy. Of these, 45 were treated from one to four days (mean 2.2 days) and 11 for six to ten days (mean 6.8 days). One other patient received nafcillin for 17 days during which time no analysis of urine was done. The patient had chronic renal failure and what appeared to be pneumonia. She received ampicillin, nafcillin (100 mg per kg of body weight per day) and gentamicin for the duration of therapy. No new fever, rash or eosinophilia was noted. Her renal function improved while she was receiving antibiotic therapy. No other manifestations of nephritis developed in these 57 patients.

Significant proteinuria was found in 42 patients (27 percent), hematuria in 27 patients (17.6 percent) and leukocyturia in 53 patients (34.6 percent). Review of the records of those with hematuria and proteinuria showed that the episodes were transient, did not occur simultaneously, and were never temporally related to declines in renal function, which would have been manifested by an increase in blood urea nitrogen or serum creatinine. In each patient, proteinuria, leukocyturia or hematuria improved while he or she continued to receive nafcillin.

Eosinophilia of 5 percent or more developed in 22 patients, but only three patients had eosinophil counts of 10 percent or more. In one patient, an eosinophilia of 18 percent, present on the initial day of nafcillin treatment, rose to 27 percent on the third day of therapy. This patient, who was anuric and on maintenance hemodialysis,

received only nafcillin for four days. The eosinophilia was not associated with fever or rash. Significant eosinophilia in two other patients (14 percent and 17 percent) was not associated with fever, rash, proteinuria or hematuria. The eosinophil count decreased to normal in one of these patients while the antibiotic drug was continued.

Ten patients had a decline in renal function during treatment. The suspected cause of this decline in each of these patients is summarized in Table 4. In seven of the ten, renal function improved while nafcillin was being administered. Of the remaining three patients, one (No. 8) experienced a rise in serum creatinine after one day of nafcillin therapy. This patient was undergoing rhabdomyolysis, and myoglobinuria and renal failure was attributed to this event. In one of the remaining two patients (No. 1), the administration of aminoglycosides, gastrointestinal hemorrhage and hypotension resulted in an increase in serum creatinine after one day of nafcillin therapy. The patient died on the seventh day of therapy and had required dopamine throughout the therapeutic regimen for maintenance of blood pressure. Postmortem examination showed renal vascular congestion and no interstitial nephritis. In the final patient (No. 7) of these ten, gentamicin was administered concomitantly with nafcillin. At no point throughout ten days of therapy was hematuria noted. Proteinuria was noted on day six but was absent at the completion of therapy. In addition, none of the other manifestations of allergy to nafcillin were present and the renal dysfunction was attributed to gentamicin. Nafcillin therapy was not discontinued in any patient because nephritis was suspected.

Seventy-four patients received nafcillin for at least six days and 28 of them received the drug for 11 days or more.

All but 12 of the 74 patients had at least one laboratory test (CBC with differential cell count, serum creatinine or analysis of urine) carried out during the last three days of therapy. Serum creatinine was the test done most frequently (in 56 patients, 76 percent).

It is possible that in the 12 patients, nephritis could have developed during the last three days of therapy; however, we feel that this is unlikely because the average duration of therapy in this subgroup was long enough (18 days) for the reac-

TABLE 3.—*Febrile Episodes in 14 Patients Receiving Nacillin*

Number of Patients	*Probable Cause*	*Comments*
4	Drug fever	Concurrent rash, eosinophilia, or both; normal findings on analysis of urine
3	Postsurgical atelectasis	No other signs of nephritis
2	Urinary tract infection	Leukocyturia and bacteriuria without other signs of nephritis
1	Relapse of *Mycobacterium intracellulare* infection	No other signs of nephritis
1	Gastrointestinal hemorrhage; cirrhosis	No other signs of nephritis
3	Indeterminate; ? drug fever	No other signs of nephritis

TABLE 4.—*Episodes of Renal Dysfunction in Ten Patients Receiving Nafcillin*

Patient Number	*Serum Creatinine (mg/dl)* *Initial*	*Peak*	*Cause of Renal Damage and Comments*
1	0.9	2.8	Gastrointestinal (GI) hemorrhage; hepatorenal syndrome; anaerobic sepsis leading to shock; concomitant aminoglycoside administration
2	0.3	1.5	Pulmonary hemorrhage; disseminated intravascular coagulation; postmortem examination: renal nephroblastoma; renal function improved while patient continued to receive nafcillin
3	1.3	2.2	Cardiorespiratory failure requiring dopamine, isoproterenol to maintain blood pressure; renal function improved while patient contined to receive nafcillin
4	1.0	1.8	Dehydration secondary to diabetes insipidus; renal function improved while patient receiving nafcillin
5	2.0	2.9	Staphylococcal sepsis, renal function improved while patient receiving nafcillin
6	5.2	8.3	Hemolytic uremia syndrome; renal function improved while patient receiving nafcillin
7	0.5	3.2	Concomitant aminoglycoside, cirrhosis, GI hemorrhage, no hematuria or proteinuria
8	1.7	3.8	Chronic ethanol abuse, rhabdomyolysis and myoglobinuria
9	1.3	1.8	Congestive heart failure; renal function improved while patient receiving nafcillin
10	0.4	1.1	Dehydration; renal function improved while patient receiving nafcillin

tion to have developed sooner, and none of the clinical findings usually associated with nephritis developed throughout the duration of therapy.

Discussion

Nafcillin was not discontinued in any patient because of a suspicion of interstitial nephritis. Further, no clinical or laboratory findings suggested that any of these patients had nafcillin-associated nephritis. It is possible that histological changes occurred in some of the patients; however, no renal biopsies were done because none were indicated.

The effect of continued therapy in patients in whom nephritis developed as a result of nafcillin doses is unreported and unknown. However, previous reports of methicillin toxicity[10] and our experience indicate that continued methicillin therapy in patients with nephritis results in progressive decline in renal function. Although this study does not rule out the possibility that nafcillin may induce nephritis, if it does occur it must appear in such a mild form (manifested solely as urinary sediment abnormalities) or so infrequently that it was not detected in this group of patients. It has been suggested that abnormal results of analysis of urine may precede the onset of renal dysfunction by a week or longer.[4] However, continuation of therapy despite these findings was not detrimental to renal function in any of the patients, regardless of the duration of therapy.

The findings previously described in methicillin-associated nephritis have been hematuria, proteinuria, leukocyturia, fever, rash, eosinophilia and renal dysfunction. In a recent literature review by Ditlove and co-workers,[5] hematuria, proteinuria and leukocyturia were reported in 93 to 97 percent of patients with nephritis, fever in 87 percent, eosinophilia in 79 percent, and rash in 24 percent of reported cases. Renal dysfunction occurred in half of the patients, a third of whom became oliguric.

Galpin and colleagues found eosinophilia, leukocyturia, fever and renal dysfunction in all of the patients in their series.[7] In our study, hematuria or proteinuria developed in many of the patients who received nafcillin therapy. It is not uncommon, however, for seriously ill patients admitted to hospital with staphylococcal infection or other underlying disorders, to have abnormal results of analysis of urine. We did not find convincing evidence in any patient in this series that these findings were a manifestation of frank interstitial nephritis. The abnormalities in urinary sediment that would suggest renal toxicity were infrequent, mild and not associated with renal failure; also, they tended to disappear even if therapy was continued.

A number of the patients received one or more additional nephrotoxic agents as summarized in Table 1. However, nephritis developed in none of the patients, whether treated with nafcillin alone or in combination with other nephrotoxic agents.

The incidence of nephritis caused by methicillin is estimated to be as high as 33 percent in patients receiving methicillin for ten days or longer, and is estimated to be at least 15 percent overall.[4] These frequencies were found in patients treated with methicillin for staphylococcal bacteremia, osteomyelitis, endocarditis and pneumonia. These are the same infections found in our patients treated for six days or longer. Assuming a 15 percent incidence, one would have expected 11 patients with nephritis in the 74 patients who received nafcillin for six days or longer. Therefore, the absence of nephritis in this group is clinically and statistically significant (x^2 value of 9.8, Yates's correction; $P<0.005$).

Some patients with hematuria in the absence of azotemia may have methicillin-induced cystitis as described by Yow[13] and Bracis.[14] Because cystoscopies were not clinically indicated or done in this series, we are unable to comment on the possible association between nafcillin and cystitis in these patients.

Neutropenia associated with nafcillin therapy, has been previously described.[15,16] In this study, 14 patients were noted to be neutropenic while receiving nafcillin. Seven of them were felt to be neutropenic because of leukemia or as a result of chemotherapy for neoplastic or collagen vascular diseases. Two additional patients were leukopenic on the day nafcillin therapy was instituted. In both cases the leukocyte counts reverted to normal during therapy. One other patient became leukopenic just before his death while receiving multiple antibiotic drugs including nafcillin. He died in septic shock.

The remaining four patients, all adults, had no reason other than nafcillin therapy for depressed leukocyte counts. The levels at nadir ranged from 2,400 to 3,300 cells per cu mm. The dosages of nafcillin in these four patients ranged from 2 to 8 grams daily. The onset of leukopenia occurred on days two, three, six, and nine of therapy, respectively. In one patient nafcillin was discon-

tinued because of leukopenia, and in this patient the leukocyte count subsequently reverted to normal. In two others, the leukocyte counts reverted to normal during therapy, and in the fourth patient, leukopenia of approximately 4,000 cells per cu mm persisted for the duration of therapy.

Conclusion

Nafcillin is clearly an efficacious antistaphylococcal antibiotic agent, at least as effective as methicillin for systemic infection,[10,11,17] and probably as effective for central nervous system infection,[18] although controlled comparisons have not been done. The difference in cost between methicillin and nafcillin has diminished substantially since the institution of the study. For these reasons and the lack of significant nephrotoxicity detected in this study, we believe that nafcillin is the penicillinase-resistant penicillin of choice.

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Management of Nosebleeds

FIRST, AFTER YOU ASCERTAIN where the bleeding [in a nosebleed] is coming from, I prefer applying cocaine as a topical anesthetic agent. . . . If [the nosebleed] is a squirter or if it is a superficial one, I would prefer to cauterize and not pack if that is possible. . . . Silver nitrate is used by many in treating nosebleeds but I have not found it to be beneficial, especially for something that is more than just a superficial blood vessel. I prefer to use electrocautery in adults, and in children I use chromium trioxide B. It must be dry powdered chromium trioxide placed on a wire applicator that has been heated red hot. The chromium trioxide, which is dry, will fuse onto the bead, and it is almost as effective as using electrocautery. And it is certainly much more effective in children who are frightened to death if you were to approach them with electrocautery. . . .

—MORRIE MINK, MD, *San Francisco*

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Chemical Warfare: Drugs in Sports

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A number of substances have been used by athletes in an attempt to improve performance in sports. The use of these substances, which are referred to as ergogenic aids, has become widespread; some pose serious health hazards. Ergogenic aids are divided into five broad classifications: physiological, physical, psychological, nutritional and chemical. It is possible, although conclusive proof is lacking, that some substances may give an athlete who takes them an advantage over one who does not. However, the health hazards posed in general by these materials far outweigh any possible advantage.

WITH THE EMPHASIS on winning in sports so predominant today at almost every level of competition—high school, intercollegiate, international and professional—it is easily understandable why an athlete might experiment with substances or methods, other than those of good basic training and coaching, in an attempt to improve athletic performance above the normal physiological level. The motivation for using such methods or substances, referred to as ergogenic aids, may come from fellow athletes, a coach, an athletic therapist or even a physician treating the competitor. An athlete may be influenced by commercial advertising or by exposure to the numerous scientific and pseudoscientific articles appearing in the literature concerning these materials. Generally speaking, however, there are very few substances or materials that will in fact improve normal physiological performance without significant health hazards associated with their use.

Materials Used

Ergogenic aids may be divided into five broad classifications: physiological, physical, psychological, nutritional and chemical. Using these broad headings we may then discuss the more common aids used by athletes in trying to improve their competitive performance.

Physiological Aids

Oxygen has been used for a number of years in an attempt to improve the supply available to the muscular system during heavy athletic activities. Indeed, the very ability of the body to transport and use oxygen may be the critical factor limiting maximum endurance capabilities. The oxygen may be taken before, during or after an event. A number of studies on the subject have been carried out and the conclusions reached are that oxygen given before a sports event may offer an advantage if taken within two minutes of performance and in short-term events of less than 30 seconds duration. Oxygen taken during an event will increase the partial pressure of oxygen in the blood significantly but its use obviously would be impractical (an athlete would have to carry an oxygen supply during the event). The use of oxygen following an all-out sports effort would be of no use unless the athlete had to return quickly to the same activity.[1]

High altitude training before a contest has been tried on numerous occasions. The rationale is that

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the relative polycythemia resulting from training at high altitudes increases the oxygen available to fatigued muscles, thereby improving muscular performance at lower elevations. There are no hard data to support this concept, although training sites are still located at high altitudes in many countries.

Blood doping (boosting) consists of the removal of approximately 1 pint of blood from a competitor three or four weeks before an endurance event. This blood is then stored under the usual sterile, refrigerated conditions. The athlete continues his or her training schedule, and in the intervening weeks before competition the normal blood volume is reconstituted physiologically. The day before the event, the athlete's own blood is reinfused into his or her own vascular tree. The added boost of red blood cells (some of which are still viable) to the reconstituted blood volume thereby gives the recipient a relative polycythemia with an increased oxygen-carrying capacity of that athlete's circulating blood volume. This would then, it is contended, act as an ergogenic aid. There have been a number of conflicting reports in the literature about this alleged positive effect of the added blood.[2-5] The possible dangers of such a procedure include mismatched transfusions, infections and clotting problems, and these alone should mitigate against such practices. Possible dangers far outweigh any possible gain from blood boosting.

Warm-ups should be a part of athletic training. They can have no adverse effects and, at least theoretically, they have a host of advantages, the most significant effect of which may well be psychological. It has been suggested that muscles become more lax during a warm-up and that the resulting elevation of temperatures within the muscles with activity increases the efficiency of the enzyme systems and allows higher metabolic activity of the muscle cells. In addition, hemaglobin releases oxygen more freely at higher temperatures.[6] Finally, there is ample evidence, albeit anecdotal, from athletes that stretching muscles before competition lessens the chance of muscle strains during competition.

Mention should be made of the use of water in athletics. Until just a few years ago it was customary for coaches to prohibit athletes from taking fluids just before or during competition because it was felt that it would impair performance. This custom in itself probably was a contributing factor to many cases of heat exhaustion and heat stroke. It is now recognized that there is no basis whatsoever for restricting water intake by athletes at any time. In addition, there is no evidence to suggest that any other substance is superior to water during competition or training. Salt and mineral loss during strenuous activity is generally not excessive and salt tablets should not be used. An athlete is much wiser to add salt to the regular diet rather than take salt before or during competition. So-called isotonic solutions are acceptable but generally not necessary to athletes who have well-balanced diets and adequate intakes of fluid. The practice of pre-event dehydration by boxers, wrestlers and weight lifters in order to "make weight" must be strongly condemned.[7] Serious health complications from such practices can result.[8]

Physical Aids

In the broad category of physical aids are those mechanical devices designed to increase athletic performance. Examples are aerodynamically designed javelins or fiberglass poles for pole-vaulters. Discussion of this type of aid is not within the scope of this article.

An interesting, even bizarre, new physical aid was reported to have been introduced at the 1976 Olympics in Montreal.[9] A European team, it has been alleged, instilled air into the rectums of their swimmers in an attempt to improve the buoyancy of these athletes. This method, aside from being no doubt very uncomfortable for the athletes, did not seem to noticeably improve the swimmers' performance. If nothing else, however, the incident does illustrate the ends to which coaches, trainers and physicians sometimes go in attempting to aid teams to win medals.

Psychological Aids

There is no doubt that the slim margin that sometimes exists between winning and losing athletes may be a psychological factor. The desire and determination to win are paramount in performance, assuming that an athlete has first achieved peak conditioning through good coaching and training methods. A coach's pep talk is a very simple example; the late Vince Lombardi, for instance, was a master at exhorting and driving his athletes to victory by this means. While psychologists once were disdained as *shrinks* by athletes, coaches, team physicians and, indeed, team managements, athletic psychologists have finally and rightfully been recognized as very im-

portant members of the sports health team. It is interesting that teams from several Eastern bloc countries, who seem to be far ahead of the Western nations in this area of sports medicine, routinely travel to international competitions accompanied by a large team of psychologists.

Nutritional Aids

In no area in sports does quackery and faddism exert a more profound effect than in the nutrition of athletes. In fact, in no other aspect of sports is ignorance more prevalent. Most athletes by nature are highly competitive and consequently susceptible to claims for aids that might supply a competitive edge. Queen bee honey, rose hips tea, various herbal preparations such as ginseng, and of course the omnipresent vitamins (particularly vitamin E), to mention but a few, are purchased in massive amounts by the athletic population. While there is no doubt that vitamin deficiencies will decrease performance, there is no evidence that supplemental vitamins taken in the absence of a deficiency will improve performance. In addition, the general athletic population does not usually suffer from vitamin deficiencies. There are indeed very few items for sale on supermarket shelves that do not contain more than adequate amounts of vitamins occurring either naturally or as additives.

Many misleading and false claims are made by some manufacturers of these coenzymes, and the vitamin industry does a multimillion dollar business annually, the majority of their products doing little else than giving our society an extremely nutritious sewage. Conversely, excesses of certain vitamins may indeed be dangerous to health. Vitamins are not, of course, used up in athletic performance and there are no scientific data showing that excesses of them increase performance in any way. Vitamin E is perhaps the best example; its advocates continue to make extravagant claims of increased performance both in the athletic and sexual fields. It is essentially a vitamin looking for a deficiency disease.[10] The vitamin hoax is a crutch upon which many athletes readily lean, especially when their performance is below that level which they hope to attain.

What has been termed "Vitamin B_{15}" by some is not a vitamin at all but a chemical substance (pangamic acid), and the name has been copyrighted.[11] Its action is unknown, it is not a vitamin, and the Food and Drug Administration has stated that "it is therefore illegal for the substance to be sold as a dietary supplement."[12] Apparently, however, its manufacturers are doing a land-office business in the sale of this product to various professional athletic teams in the United States.[13]

Traditional ideas about the composition and importance of a pregame meal have changed. While at one time many football players would insist on a large steak three hours before competition, the medical profession has finally convinced coaches that steak will in fact still be in the stomach following the game. If the steak is to be eaten it should be following the game. An athlete should eat a light, balanced, easily digestible carbohydrate meal three hours before the event—for instance, pancakes, waffles or spaghetti. Liquid protein nutrient preparations taken before an event are of no immediate value to an athlete. Fluids with high sugar content should not be taken just before competition. Such preparations are of no use during competition, delay emptying of the stomach, and will lead to hypoglycemia due to the demands of the sudden large insulin release and the demands of the contracting muscles during the event on the glycogen supplies. Conversely, starvation for a few days before an event in an attempt to "make weight" should be discouraged. Not only is this practice harmful to health because of the accompanying loss of protein, glycogen, minerals and enzymes, but the performance of the athlete will be decreased.[14]

The carbohydrate loading diet has become an approved dietary manipulation which has shown evidence of improving athletic performance in endurance events. An athlete trains and eats normally until seven days before an event, at which time the training diet is modified for the next three days so that it is composed almost exclusively of protein and fat. The athlete continues to train but on a reduced scale and the muscles are gradually exhausted of glycogen stores in this manner. For the final three days before the competition only carbohydrates are eaten and the theory is that the muscles overreact by storing larger than normal amounts of glycogen. Training is further reduced during these three days with no training being carried out the day before and the day of competition.[15]

Chemical Substances

Under this heading are included all of the chemical substances used as ergogenic aids, largely those pharmaceutical products that are

used (and abused) by athletes. These are the substances that pose the most severe health hazards and at the same time are those most prevalently used in sports. Generally speaking, these materials are specifically prohibited at the international amateur (and in some cases, professional) level. Their use has been widespread in the past and has contributed directly to many deaths.[16] Indeed, members of the lay press, some of whom seem to believe that all athletes in international competition resort to drugs, have on occasion labeled the Olympics as "chemical warfare." A number of sports reporters have written to the effect that medals in competitive sports should be given to the drug houses. It was the suspected widespread use of these products, with their serious hazards to health and related reported deaths, that led the International Olympic Committee (IOC) to legislate against their use at the international amateur level. This led to the institution of urine testing for competing athletes at all levels of international amateur sports, which was carried out in the winter and summer Olympic Games in 1968. An up-to-date list of those substances labeled as forbidden was published just before the Lake Placid Games[17] and is shown in Table 1. Each competing nation was supplied with this booklet before the competition.

Psychomotor Stimulant Drugs

The use of psychomotor stimulant drugs (listed under section A in Table 1) may constitute the major drug-related problem in athletics. There is no doubt that they have been widely used in the past but it is hoped that most athletes now realize their dangers and that usage is declining. There is ample evidence (for example, in many of the autobiographies of former athletes) that these drugs have been abused in sports particularly by professional athletes. A common statement is that "the bennies were right next to the salt tablets in the training room." Apart from the health hazards associated with these drugs, which will be discussed, there are important legal aspects. Several law suits in the recent past have been brought by athletes against team physicians and managers for supplying these drugs to them ad lib. It has been claimed by the athletes that they became dependent on the drugs as a result of this easy availability. At least one physician recently has had his license to practice temporarily suspended because he administered drugs of this nature to athletes. In addition, occasional reports can be found in the news media about professional athletes who have been caught trafficking in these materials.

The use of psychomotor stimulant drugs may in one sense improve athletic performance because the drugs can make an athlete more alert initially and shorten reaction time. However, they also obscure an athlete's physiological fatigue level. That is to say, they allow an athlete to "run the red light" because they mask the normal symptoms of fatigue. This in itself of course can be very dangerous, and obviously could easily prove counterproductive for an athlete in the long term. In addition, use of the drugs can easily mask a

TABLE 1.—*List of Doping Substances*

A. Psychomotor stimulant drugs
e.g.
amphetamine
benzphetamine
chlorphentermine
cocaine
diethylpropion
dimethylamphetamine
ethylamphetamine
fencamfamine
meclofenoxate
methylamphetamine
methylphenidate
norpseudoephedrine
pemoline
phendimetrazine
phenmetrazine
phentermine
pipradol
prolintane
and related compounds

B. Sympathomimetic amines
e.g.
chlorprenaline
ephedrine
etafedrine
isoetharine
isoprenaline
methoxyphenamine
methylephedrine
and related compounds

C. Miscellaneous central nervous system stimulants
e.g.
amiphenazole
bemigride
doxapram
ethamivan
leptazol
nikethamide
picrotoxine
strychnine
and related compounds

D. Narcotic analgesics
e.g.
anileridine
codeine
dextromoramide
dihydrocodeine
dipipanone
ethylmorphine
heroin
hydrocodone
hydromorphone
levorphanol
methadone
morphine
oxocodone
oxomorphone
pentazocine
pethidine
phenazocine
piminodine
thebacon
trimeperidine
and related compounds

E. Anabolic steroids
e.g.
methandienone
stanozolol
oxymetholone
nandrolone decanoate
nandrolone phenylpropionate
and related compounds

Source: Extracted from IOC Medical Controls, XIII Winter Games, Lake Placid, NY, 1980.

serious injury by making it appear less severe. Such drugs can also make an athlete more hostile and aggressive—which may account for much of the unnecessary brutality and rough play seen in professional hockey, American football and some other sports.

A large number of studies carried out with these drugs have been reported in the literature, starting in the 1950's. In one of the classic reports by Karpovitch[18] the investigator concluded that there was no real beneficial effect derived from taking these stimulants. Another report in the same year by Smith and Beecher[19] suggested that perhaps there was an advantage to taking these materials. (This latter study has come under a great deal of scientific scrutiny and criticism.) A recent report in the literature (1980) is by Chandler and coworkers,[20] who indicated that there was probably no substantial improvement of performance with the use of such stimulants.

One of the most powerful central nervous system stimulants, caffeine, has become very popular with athletes. In a study carried out at the 1976 Olympic Games in Montreal, Laurin and Letourneau reported finding significant amounts of caffeine in a large number of the 2,080 urine specimens tested from competing athletes.[21] This material is not banned under IOC rules because it appears so commonly in normal diets in such products as tea, coffee and cola drinks. A recent study on caffeine has also indicated that there is an increased work output with increased ingestion of caffeine due to increased mobilization of fat, an increase in plasma free fatty acids and an increased rate of lipid metabolism.[22]

In regard to another stimulant, cocaine, the author knows of no scientific studies carried out to assess this drug's effects on athletic training or competition.

Sympathomimetic Amines

The sympathomimetic amines (section B, Table 1) are the drugs that cause the most problems to physicians associated with international athletic competitions where testing for drugs is carried out. These are the substances found in common cold remedies, as well as in nasal and optical decongestants. These in fact are the materials that so often turn out to be the cause of positive results of drug tests and lead to disqualification of athletes and in some cases loss of medals.[23] All physicians should be aware that these materials are among those tested for by the IOC. Indeed, a gold medal was lost by an American swimmer in the 1972 Olympics because of a positive test finding for such a drug. It is to be remembered that the urine tests carried out by the IOC are qualitative only and not quantitative; they do not distinguish between therapeutic and so called doping doses. The mere presence of a minute amount of the material is enough to disqualify an athlete. Before the Montreal Olympics in 1976 a double-blind study was carried out on one of the constantly used antiasthmatic compounds containing ephedrine.[24] This study showed no significant improvement of performance in those athletes studied. It is interesting that in the original articles on the subject in the 1950's and 1960's it was suggested that such materials did improve athletic performance. However, in the more recent studies of the 1970's (which would seem to be of greater scientific validity), no significant or appreciable improvement in performance has been shown to occur with the use of these materials.

Miscellaneous Central Nervous System Stimulants

A number of miscellaneous central nervous system stimulants are given in the IOC listing. One example is strychnine which, surprisingly enough, has been used as a stimulant by athletes, particularly cyclists. An American cyclist was reported to have been found using this material in the 1904 Olympics in St. Louis,[16] and the author has recently seen European vitamin preparations containing strychnine used by six-day cyclists.

Narcotic Analgesics

The narcotic analgesics are of course prohibited by the IOC, and their use is clearly dangerous. A number of deaths have been reported from the use of these materials by athletes.[16] Apart from their serious hazards and addictive qualities, they are dangerous because they may allow an athlete to compete with a serious injury by masking the symptoms.

Marijuana is not on the IOC doping list; however, studies have been carried out on its effect on performance in athletics. One fairly recent study by Steadward and Singh reported no significant difference in handgrip strengths, vital capacity and expiratory flow rate in subjects after smoking a placebo or marijuana.[25]

Anabolic Steroids

Anabolic steroids, unfortunately, are widely used in weight lifting and throwing sports. Their

use is extremely common at high school, university, professional and international athletic levels. Regrettably, the lay literature has reported these substances as being responsible for substantially increasing muscle size and consequently strength. The substances do stimulate the synthesis of cellular protein and have an interesting history. They are reported to have been used in World War II by German troops to improve their aggressiveness and strength in battle. Following World War II they apparently were used to help restore the wasted bodies of concentration camp victims and prisoners of war. The medical profession did use them briefly in treatment of osteopenia but use was later abandoned in that area. Steroids have been used extensively in the animal sciences field to increase muscle mass, with its obvious economic advantages in cattle.[26] It has been found, however, that diethylstilbesterol is much more effective in livestock than the anabolic steroids. It is to be noted also that these materials are not used in cattle destined for breeding purposes but rather those destined for slaughter. (The use of these materials in cattle has declined because of recent legislation prohibiting further production of the hormones previously manufactured for this purpose.)

Anabolic steroids still find a useful role in certain medical conditions such as metastatic cancer, aplastic anemia and chronic renal failure. Shahidi has recently reported that these materials given with parenteral iron will significantly increase hemoglobin levels in patients with chronic renal failure.[27]

Many athletes have eagerly seized upon the use of these products, assuming that these materials by increasing muscle size will raise their performance above that level achievable through normal physiological conditions and training. Vast doses of these materials apparently are taken ad lib.

Most of the studies that purport to show beneficial effects of anabolic steroids in athletics should be subjected to very careful scrutiny. For example, some of these studies have not used true double-blind methods. Moreover, the amounts of the materials used in the studies usually are not comparable with the amounts actually used by athletes. Anabolic steroids are, in fact, extremely dangerous; their use by athletes has been condemned by the American College of Sports Medicine.[28] The health hazards associated with the taking of these materials are frightening. One of the effects is salt and water retention which leads to hypertension. A host of other complications have been reported, including hepatitis, jaundice and cancer of the liver. In men, loss of sexual drive, impotency and even testicular atrophy have occurred. In women, hirsutism and deepening of the voice are possible side effects. The use of these compounds by immature humans may result in early skeletal maturation.

These materials do apparently increase appetite and dietary intake. There is an associated increase in training and conditioning at the time these materials are taken and there is no doubt that an increase in muscle size *(bulking)* does occur. Some investigators feel it is these factors that lead to increased muscle size rather than any direct anabolic effect. One of the most recent comprehensive articles published on this subject reported as follows: "We believe, however, that the existence of an anabolic action, which must be the principal basis for consumption by athletes, should be regarded as an open question."[29] On the other hand, a number of published studies have tended to support the thesis that these compounds do improve muscular performance. Moreover, anabolic steroids are highly acclaimed in the athletic world, and this in itself can produce a definite beneficial, psychological effect on athletes taking them. All in all, however, the serious health hazards associated with their use far outweigh any potential gain that might be expected.

Other Chemical Substances

There are other materials taken by athletes in an attempt to improve performance. Beta-adrenergic blockers are an example. These materials have been used by musicians, ballet dancers, public speakers and other persons in whom anxiety and tension may mitigate against a good performance. While these substances may be of some help in reducing anxiety associated with stress, there is no real evidence that their use will increase athletic performance.[30] Diuretics, another example, have been used for a number of years in combination with water and food restriction in sports where weight is a factor. This approach,[7,8] mentioned earlier, should be condemned by physicians, coaches and trainers.

Alkalinizers have been reported as being a possible ergogenic aid.[6] The technique involves ingestion of an alkaline salt following meals for a

few days before and following a competition. Because lactic acid is formed as a result of intensive exercise, it is thought that the use of these substances would result in a higher pH to start with so that the athlete would be able to make more lactic acid before exhaustion and presumably be capable of a greater work output. It has been reported in the doping manual of the IOC that the use of alkalinizers can, by raising the urine pH, lead to a much slower excretion rate in the urine of the by-products of the stimulants occasionally used by athletes. Alkalinizers have also been used in the past in a vain attempt to mask the use of stimulants on this basis.[16]

Alcohol has long been used by competitors in athletic events, in modern times particularly by cyclists, rifle sharpshooters, and participants in biathalons. It is used because of its possible tranquilizing effect, it is a readily available source of carbohydrate and it acts as a diuretic in small amounts. However, alcohol does delay reaction time, and probably most often detracts from performance. It is occasionally tested for at the international level. It can have serious health hazards by masking the normal warning symptoms of fatigue and disinhibiting athletes.

Conclusion

There is no question that the use of ergogenic aids has become widespread among athletes. The increased social, political and economical rewards associated with success in sports increasingly force athletes to improve their performance. An athlete may be persuaded by a friend, fellow athlete, coach, manager, trainer or physician, or even an overenthusiastic parent, to resort to the use of unethical and dangerous practices in an attempt to win. It is apparent, however, that any possible athletic advantage to be gained from the use of any of the various chemical products is far outweighed by the serious health hazards associated with their use. Physicians involved in sports medicine must be aware of the facts related to the use of ergogenic aids and should make an active effort to educate athletes. A physician who makes potentially dangerous chemical substances available to an athlete or a team should be penalized.

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Nutritional Aspects of Ascorbic Acid: Uses and Abuses

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Ascorbic acid in physiological doses is essential for the normal functioning of the human body. Larger doses are required to treat a severe deficiency of vitamin C intake, as in the case of scurvy. Occasionally, massive doses may be required to treat a metabolic defect involving ascorbic acid. There has been some mention of megadose therapy with ascorbic acid for the prevention of colds, the improved healing of wounds and even the treatment of cancer, but no acceptable scientific data have been presented. In fact, in a few instances, such therapy has proved injurious.

PREVENTION AND CURE of scurvy are the major physiological and pharmacological functions of ascorbic acid. Though scurvy was described in ancient medical records *(Ebers Papyrus* about 1500 BC), a method of prevention was not discovered until James Lind carried out his shipboard experiments with citrus fruits, which he published in 1753.[1,2] He wrote:

> I come in the next place, to an additional extremely powerful cause (of scurvy), observed at sea to occasion this disease, and which concurring with the former, in progress of time, seldom fails to breed it. And this is, the want of fresh vegetables and greens; either as may be supposed, to counteract the bad effects of their before mentioned situation; or rather and more truly to correct the quality of such hard and dry food as they are obliged to make use of. Experience indeed sufficiently shews, that as greens or fresh vegetables, with ripe fruits are the best remedies for it, so they prove the most effectual preservatives against it, and the difficulty of obtaining them at sea, together with a long continuance in the moist air, are the true causes of its so general and fatal malignity upon that element.

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Hexuronic acid was isolated in 1928 by Szent-Györgi[3] from orange juice, cabbage juice and the adrenal glands of oxen. But it was not until it was identified as vitamin C, the antiscorbutic substance, by Waugh and King[4] in 1932, and synthesized by Von Reichstein[5] in 1933 that the chemical picture was complete.

Of all members of the animal kingdom, only primates (including humans), guinea pigs, red-vented bulbuls, fruit-eating bats, rainbow trout and coho salmon are dependent on dietary sources of vitamin C.[6-9] They lack the enzyme system necessary for the conversion of 3-keto-1-gulonate to 1-ascorbate. One may infer that during the evolutionary process, these creatures had such excellent dietary sources of vitamin C that they no longer needed the chemical conversion that otherwise is present universally in the animal kingdom.

Ascorbic Acid Therapy for Scurvy

Scurvy still occurs in malnourished persons, particularly in those who live alone and do not prepare proper meals for themselves or who fre-

quently eat in restaurants, as well as in infants on unsupplemented milk diets. To understand the disease better, several investigators[10-13] have studied volunteers (often themselves) on vitamin C-free diets. The purpose has been to determine the rapidity and sequence of development of clinical manifestations of scurvy and to correlate biochemical measurements with these manifestations.

Table 1 lists clinical manifestations of scurvy in adults. In the experiments of Hodges and his co-workers,[13] fatigue and aching sensations, especially in the legs, and mild general malaise began about the same time as the first petechial hemorrhage appeared. These manifestations occurred on the 26th day of vitamin C deprivation. (In other trials these symptoms occurred later.[10]) On the 45th day of the trials conducted by Hodges and associates, the first perifollicular hemorrhage was seen as well as ecchymoses induced by minor trauma. (Figure 1 shows extensive ecchymoses in a patient with scurvy.) Perifollicular hyperkeratoses were noted on the calves of the subjects between the 60th and 88th day. The hairs on the buttocks of one subject were coiled and fragmented, a sign frequently seen in patients with naturally occurring disease.

TABLE 1.—*Clinical Manifestations of Scurvy in Adults*

Weakness, fatigue, listlessness
Aching in bones, joints and muscles
Hyperkeratoses around hair follicles
Fragmented, coiled, ingrown hairs
Perifollicular hemorrhages
Petechiae and ecchymoses on arms and legs
Conjunctival hemorrhages
Muscle and joint hemorrhages
Subungual splinter hemorrhages
Swollen blue-red friable gums around teeth
Teeth that loosen and fall out
Poor wound healing
Scleral icterus and anemia
Fever, convulsions, shock and death

Figure 1.—Extensive confluent ecchymoses on the legs of a patient with scurvy. (Reprinted from Vilter[7]; with permission of Academic Press.)

TABLE 2.—*Clinical Manifestations of Scurvy in Infants*

Listlessness, irritability, failure to thrive
Assumption of fetal position because of tender extremities
Apprehension when handled
Subperiosteal hemorrhages
Scorbutic rosary
Petechiae and purpura
Blue-red swollen gums around erupting teeth
Visceral and brain hemorrhages
Cyanosis, convulsions, shock and death

Between the 84th and 91st day, small superficial red spots that appeared to be conjunctival hemorrhages developed in each eye near the limbus. Between the 76th and 91st day the gums became congested, swollen and blue-red and bled easily after the teeth were brushed. Wounds failed to heal only after prolonged deprivation (180 days in Crandon's experiments[10]); before that, there was no problem with the healing of the experimental wounds.[13]

None of the experiments were carried beyond this point. Under natural circumstances, should severe ascorbic acid deficiency persist, massive subcutaneous and intramuscular hemorrhages may develop along with hemarthroses. Teeth will loosen and fall out. Neuritis, caused by blood escaping into nerves may appear, jaundice of a hemolytic type may develop, the temperature may rise to 38.9°C (102°F), peripheral cyanosis and livedo reticularis may develop and, finally, Cheyne-Stokes respirations, convulsions, shock and death may supervene.[14]

The development of the disease in infants is shown in Table 2. The first symptoms are listlessness, anorexia, irritability and failure to thrive. As hemorrhage begins to develop in muscles and under the periosteum, the infant assumes a fetal position, with legs drawn up on the abdomen, and will be very irritable when handled. Costochondral junctions loosen and the sternum sinks, enlarging the costochondral junctions, and thereby producing the scorbutic rosary. Petechiae, purpura, blue-red swollen gums around erupting teeth, bleeding from the gastrointestinal and genitourinary tracts and into the brain, are followed by convulsions, shock and death.[15]

Anemia did not occur in adults during the course of the deprivation experiments, but when scurvy occurs under natural circumstances, nor-

mocytic normochromic anemia develops when there has been sufficient acute loss of blood; microcytic hypochromic anemia occurs when chronic blood loss and infections have predominated; and macrocytic, megaloblastic anemia develops when folic acid deficiency is combined with ascorbic acid deficiency.[14-17] There is still only circumstantial evidence that ascorbic acid has a direct effect on blood formation.[14,18]

A roentgenogram of the bones of a developing child,[19,20] but not an adult,[21] may show characteristic features (Figure 2). A crack at the anterior corner of the lower end of the tibia and at the outer corner of the lower end of the radius is called "the corner sign." Bleeding under the periosteum through these cracks leads to subperiosteal hemorrhages, which, during the healing process, may calcify. Another sign of scurvy is the "white line," a dense zone of provisional calcification at the epiphyseal end of the diaphysis of the tibiae and radii. Shaftward is a zone of rarefaction. The bones frequently have a ground-glass appearance, and epiphyses look like halos. The bones of adults with scurvy may appear to be osteoporotic, but otherwise are unaffected.[21]

Laboratory tests may be consistent with a diagnosis of scurvy but are not proof positive. The ascorbic acid level in the buffy coat of the blood, which is normally greater than 20 mg per dl, falls below 4 mg per dl after 80 days of dietary deficiency, about the time the first scorbutic symptoms appear. More severe restriction of dietary vitamin C may bring about these changes earlier. Testing how completely ascorbic acid has saturated tissue by measuring the amount of the vitamin in the urine after a loading dose is complicated and adds nothing to the diagnosis. By tagging the body pool of ascorbic acid with carbon 14, it is possible to determine pool size at the time when the first clinical signs and symptoms of scurvy appear.[22] A reduction from a normal body pool of 1,500 mg to 300 mg seems to be consistent with a diagnosis of scurvy.

Biochemical Function of Ascorbic Acid

The exact biochemical function of ascorbic acid is not known. It is a reducing agent and undoubtedly maintains certain enzymes and their cofactors in an active state. For instance, it maintains folic acid reductase in a state of activity. If folate metabolism is impaired because the dietary intake of folic acid is suboptimal, megaloblastic anemia may occur.[23] Ascorbic acid also prevents the

Figure 2.—Roentgenogram illustrating the scorbutic white line, halo epiphysis, and corner sign in an infant with scurvy. (Reprinted from Vilter[7]; with permission of Academic Press.)

oxidation of 5-methyltetrahydrofolic acid to inactive 10-formyl folic acid. Iron in food is reduced to the ferrous state in the jejunum by ascorbic acid as well as by other reducing agents, facilitating absorption.[24] Ascorbic acid is an essential cofactor for peptidyl proline and lysine hydroxylases that facilitate the hydroxylation of proline and lysine after these amino acids have been incorporated into the peptide chains of collagen, thus promoting the development of cross linkages and stabilization of the triple helix.[25-28] The postulated mechanism is the maintenance of copper and iron in a reduced state.[29] Ascorbic acid is also essential for the formation of intercellular ground substance and probably for some of the components of complement that have amino acid sequences similar to collagen.[30] A defect in the formation of mucopolysaccharides and glycoproteins has been postulated that could adversely affect capillary basement membranes. Collagen formed by scorbutic animals is not as effective a platelet-aggregating agent as is normal collagen, a defect which might contribute, along with fragile vessels, to the tendency for scorbutic patients to bleed.[31-33]

When ascorbic acid is lacking, there are abnormalities in several other hydroxylation reactions, such as in conversion of tyrosine to homogentisic acid,[34-36] tryptophane to 5-hydroxytryptophane[37] and dopamine to norepinephrine.[38] Thus, the formation of the chemical mediators norepinephrine and serotonin could be adversely affected. Vascular responsiveness may be impaired because of a variety of abnormalities.[39,40] In infants and children with scurvy, a condition called tyrosyluria may occur, particularly after a test dose of tyro-

sine or phenylalanine has been given. Parahydroxyphenyl pyruvic and lactic acids appear in the urine because of decreased activity of their oxidases.[41,42] This defect has also been found in infants with marasmus.[43]

The adrenal gland is an organ usually very rich in ascorbic acid. Because, during the development of scurvy, the supply is severely depleted, investigators have suggested that adrenal function might be impaired. Only minimal evidence has been found to support this hypothesis, however.[44-48] Some investigators have reported that blood cholesterol levels are low in scurvy and rise when ascorbic acid is given.[49-51] Others have reported that in scorbutic guinea pigs, the activity of cholesterol 7-α-hydroxylase, an enzyme that is important in the conversion of cholesterol to bile acids, is low.[52-55] This tends to keep the cholesterol high and the rate of excretion of bile acids and the size of the bile acid pool low. It has been reported that in most human beings with latent vitamin C deficiency and with elevated plasma cholesterol and triglycerides, resaturation of the tissues with ascorbic acid can substantially lower the triglyceride and cholesterol levels.[53,56] On the other hand, a population survey failed to show any correlation between levels of ascorbic acid in blood and cholesterol in plasma.[57]

Other Uses of Ascorbic Acid

Patients with Chédiak-Higashi syndrome, a condition characterized by morphologically bizarre and unresponsive leukocytes, have been treated with ascorbic acid[58] because this vitamin has been shown to enhance the chemotactic responsiveness of human monocytes and neutrophils to endotoxin-treated serum, and to elevate cyclic guanosine monophosphate of monocytes.[59] Improvement was noted in chemotactic migration and bacteriocidal activity. The improvement occurred as the level of cyclic adenosine monophosphate (AMP) fell and that of cyclic guanosine monophosphate (GMP) rose. The leukocytes of a patient with hyperimmune E syndrome showed improved granulocyte and lymphocyte function after treatment with ascorbic acid.[60]

There is also laboratory evidence that ascorbic acid plays an important role in certain manifestations of the immune response,[61] particularly in facilitating leukocyte mobility as noted above. Normal leukocytes use ascorbic acid rapidly during infection, and the level of ascorbic acid in leukocytes is frequently below average in a variety of situations with which depressed immunologic function is associated.

About 10 mg of ascorbic acid per day will prevent and sometimes will cure scurvy,[62] 45 to 60 mg per day will maintain tissue saturation[22] and 100 mg three times a day is the dosage usually used for the treatment[6] of scurvy. Despite these facts, ascorbic acid megadose regimens for many different diseases still attract a great deal of attention and controversy.

Megadose Therapy With Ascorbic Acid

Megadose therapy with vitamin C and many other essential nutrients is not new, but certain considerations emphasized by some investigators during the early 1970's popularized the practice. They reported that if human beings were able to synthesize ascorbic acid as mice, rats and rabbits can, they would produce between 2 and 20 grams of the vitamin daily. In addition, if a chimpanzee were the size of a human being yet continued to eat his own traditional diet, the ascorbic acid intake would be in the range of grams rather than milligrams.[63-65]

The proponents of the hypothesis argued that animals synthesize or eat various compounds in the amounts needed for good health. This hypothesis is not necessarily true. Many items of physiological importance are synthesized or eaten in great excess, and are eliminated rapidly from the body as is vitamin C when plasma levels exceed the renal threshold of 1.4 mg per dl. Other substances, like cholesterol, may be stored and cause damage in the process. Megadoses of vitamin C do not produce any better tissue or leukocyte saturation than do physiological dosages such as 60 to 80 mg per day.[22,66]

Nonetheless, there have been many recent reports of the benefits of megavitamin therapy for the prevention of the common cold, the treatment of cancer and the healing of wounds, as well as to increase longevity. However, there are no properly controlled studies that substantiate these claims.

Wound Healing

Surgeons have been giving postoperative patients 1 to 2 grams of ascorbic acid intravenously daily to accelerate and improve wound-healing[67,68] beyond what might be expected with physiological doses. The rationale is that wounds in scorbutic guinea pigs and humans heal poorly, and wounds

in normally nourished, burned guinea pigs heal with the histological appearance of wounds of scorbutic guinea pigs.[69] It is recognized that the stress of the postoperative state depresses the level of ascorbic acid in blood, urine and tissue, and that healing wounds seem to sequester more than the usual amount of ascorbic acid found in other tissues. Nonetheless, no unusual losses of ascorbic acid through urine, stool or blood have been identified, and little efficacy for vitamin C in megadose amounts has been shown. A modest increase in ascorbic acid intake during the postoperative period can be defended,[70,71] but studies of wound healing during ascorbic acid depletion and repletion in human volunteers lend no support to the concept that megadose therapy does more than physiological doses. Wounds healed quite well early in the course of experimentally induced human scurvy and during the phase of repletion with between 4 and 8 mg of ascorbic acid per day.[13]

Prevention of Colds

There is laboratory evidence that ascorbic acid plays an important role in certain manifestations of the immune response, particularly in facilitating leukocyte mobility,[61] such as has been noted in Chédiak-Higashi syndrome, but there is no solid scientific justification for the consumption of megadoses of vitamin C to prevent or cure infections. Berry and Darkel[72] surveyed trials of vitamin C as a prophylactic against infection, especially the common cold, and found no satisfactory evidence that any increase in recommended dietary allowances is necessary. In 1975, Dykes and Meier[73] found no evidence to support claims of clinically important efficacy, and Chalmers and co-workers,[74,75] after running a controlled experiment themselves on the prophylactic effect of vitamin C against the common cold, considered only 8 of 15 reports scientifically acceptable, and these 8 were not convincing. Many others working on this and related megadose subjects have reviewed the evidence and found it wanting.[76,77]

Studies of Navajo Indians,[78] which at first were reported to be supportive of the claims for therapeutic efficacy in preventing colds, were reviewed and reassessed as showing no such benefit. Recent studies such as the trial involving 674 marines who took 2 grams of ascorbic acid a day for eight weeks showed no difference in incidence of colds, though the group taking ascorbic acid rated cold symptoms less severe. The latter observation, possibly based on an observed antihistamine-like effect of large doses of ascorbic acid,[79] was not reflected in fewer sick calls, difference in symptom complexes or in training days lost.[80]

Miller and associates[81] studied the effect of large doses of vitamin C on cold prevention in twins and found no significant overall treatment effect. The response was not uniform, however, for treated girls in the youngest two groups had significantly shorter and less severe episodes of illness. The same was true of the youngest group of boys, but the differences were not great and the significance was unclear. In this same study, the growth rate for the youngest group of boys on the lowest dosage was 1.3 cm greater in five months than in the untreated group. This was not true of all the investigational subjects. It is possible that the other groups counter-balanced the youngest, raising serious doubts about the study's validity.

Treatment of Cancer

The case for megadose therapy of cancer patients[82] is based on the following observations and hypotheses: (1) Ascorbic acid is concentrated in neoplastic tissue, depleting normal tissue stores. (2) Ascorbic acid is essential for the integrity of intercellular matrix and, therefore, may be important for resistance to malignant infiltrative growth, and possibly for the inhibition of tumor enzymes that promote invasiveness. (3) Ascorbic acid is essential for the formation of new collagen and, therefore, may help a cancer patient enmesh his own tumor cells in a barrier of new fibrous tissue. (4) Because ascorbic acid potentiates the immune response in several ways, one might expect the immune system to perform its functions more efficiently and hold in check the growth of tumor cells. (5) Ascorbic acid may protect against a number of chemical and physical carcinogens by participating in their destruction through its capacity to reduce biologically active compounds. Clearly these are hypotheses and speculations, and do not constitute evidence of efficacy in treating cancer in humans.

The clinical trials that are said to support the anticancer hypothesis, unfortunately, use historical controls for comparison and are therefore unacceptable. The authors of one paper supporting the cancer hypothesis stated, "No properly designed clinical trial has yet been carried out to assess the value of supplemental ascorbic acid in general

cancer management."[83] Shortly thereafter, a double-blind controlled trial using placebos, involving 60 paired cancer patients in each group, showed no benefit from a dosage of 10 grams of ascorbic acid per day.[84]

In addition to the common cold and cancer, megadoses of ascorbic acid have been recommended for the control of mental dysfunction including schizophrenia, for detoxification of heavy metals, to increase longevity[77] and to acidify the urine.[85,86] In conjunction with mandelamine, 3 to 6 grams of ascorbic acid daily will acidify the urine without causing a significant fall in blood pH, but there are no acceptable scientific data supporting the other hypotheses.

Possible Side Effects of Megadose Vitamin C Therapy

Though ascorbic acid is considered to be nontoxic, certain problems may occur occasionally in patients taking megadoses for a long time.[87] It appears that mechanisms for destruction and elimination of ascorbic acid are potentiated by the megadoses and that these potentiated mechanisms do not return to normal immediately after the megadoses are discontinued. It is possible for scurvy to occur under these circumstances in patients in whom megadoses have been suddenly discontinued.[88] Scurvy has been reported in an infant born of a mother who had been taking megadoses of ascorbic acid.[89]

Ascorbic acid is metabolized through oxalic acid; thus, in those prone to oxaluria, oxalic acid stones may occur.[90] In some unexplained manner, uricosuria and uric acid stones also occur.[91] Hemolytic crises have been reported in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency and with sickle cell anemia.[92,93] Sensitivity of erythrocytes to peroxide hemolysis is increased[94] and low blood levels of vitamins B_{12} have been reported in subjects on megadoses for several years.[95] Fifty percent to 90 percent of vitamin B_{12} in the diet has been reported to be destroyed by ascorbic acid megadoses.[96,97] These observations have been explained as destruction of vitamin B_{12} during the assay rather than in vivo destruction.[97,98] Tests for blood in the stool may become falsely negative as may the Testape results for glucose, although the Clinitest may show falsely positive results.[99]

Large doses of ascorbic acid given to patients with thalassemia or hemochromatosis will mobilize much more iron for chelation by desferroxamine than could be expected when only desferroxamine is given.[100] There is danger, however, that more iron may be mobilized than desferroxamine can chelate, resulting in tissue damage.

The only reasonable indication for the prescription of megadoses of ascorbic acid is a metabolic defect, that is, a deficient or defective enzyme that can be activated only by massive doses of ascorbic acid. An example is the type VI variety of the Ehlers-Danlos syndrome, due to impaired collagen lysyl hydroxylase.[101] A dosage of 4 grams of ascorbic acid per day resulted in improvement in muscle strength, corneal growth, pulmonary residual volume and bleeding time. Urinary hydroxylysine increased while ascorbic acid was being given and decreased when it was discontinued. A chronic ulcer healed while ascorbic acid treatment was given over a two-year period. Hydroxylysine content of the skin, however, did not change.

Summary

Ascorbic acid in physiological doses is essential for the normal function of the human body. Occasionally, massive doses may be necessary to compensate for a defective enzyme system, but otherwise megadoses of the vitamin for the prevention of colds, healing of wounds and therapy of cancer are ineffective and, in a few cases, dangerous.

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Chemoprophylaxis—A Misconception

THE IDEA OF preventing infection by chemoprophylaxis was based on a misconception. The idea was that if a drug was so good that it could eliminate bacteria that had already established themselves and were producing disease, then it should be very effective in eradicating bacteria just after they had been implanted or in preventing them from getting implanted. But it turns out that this is not true. . . . It is very simple to lay down two distinct and never deniable rules for the use of chemoprophylaxis. The first rule is as follows: If the purpose of the chemoprophylaxis is to prevent invasion by a single organism that is sensitive to the drug being given, the chances of success are 100 percent. There is a second, contrary rule: If the purpose of the prophylaxis is to prevent invasion by every organism in a patient's internal and external environment, the chances of failure are 100 percent. In our own experience with 800 patients with measles (half of whom got penicillin or other drugs for prophylaxis, the other half of whom did not), there was a higher incidence of infections in those who got the penicillin. Even more threatening was the fact that the infections were from unusual organisms. Up to that point in my experience, I had never seen an acute otitis media due to *Proteus vulgaris.*

—LOUIS WEINSTEIN, MD, *Boston*

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Refer to: Locksley R: Fuel utilization in marathons: Implications for performance—Medical Staff Conference, University of California, San Francisco. West J Med 133:493-502, Dec 1980

Fuel Utilization in Marathons: Implications for Performance

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *In keeping with our yearly tradition, this Medical Grand Rounds will be presented by our chief resident. Dr. Richard Locksley will discuss fuel utilization in marathons, and its implications for performance. This is not just of academic interest to Dr. Locksley because he has run the marathon in less than 2 hours and 30 minutes himself.*

DR. LOCKSLEY:† Marathons have become increasingly popular races in the United States, with more than 50,000 men and women runners completing such races in 1979. The high intensity and prolonged duration of these grueling 42 km (26.2 mile) road races clearly illustrate the role of body fuels in sustained exercise. Furthermore, a study of high-intensity prolonged aerobic exercise can shed light on many facets of intermediary metabolism that are broadly applicable to other hypercatabolic states, such as occur in trauma, starvation or during surgical procedures. Recent data increasingly suggest several metabolic benefits of long-distance running.[1,2] The following review was undertaken to provide background for these emerging concepts, as well as to assist runners preparing for such an event.

The energy expenditure of a marathon is roughly 60 kcal per km (96 kcal per mile). Pace has little effect on the caloric cost per mile.[3,4] The intensity of a competitive marathon is between 70 percent and 80 percent of the maximal oxygen uptake (Vo_2 max). Vo_2 max defines the point at which oxygen consumption and combustion can no longer keep up with the breakdown of adenosine triphosphate (ATP) by contracting muscles; that is, when oxidative (or aerobic) exercise can no longer continue. Thus, a marathon is an aerobic event. This contrasts to the sprint events, in which ATP is supplied principally by anaerobic glycolysis and consumption of the stored phosphagens ATP and creatine phosphate.

The fuel stores in an average man in the resting postabsorptive state are given in Table 1. At the pace of a competitive marathon, if only carbohydrate stores (glucose and glycogen) were used, the blood glucose would be consumed in less than half a mile, the hepatic glycogen by two miles, and the entire muscle glycogen supply in an

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†Richard Locksley, MD, Chief Medical Resident.

ABBREVIATIONS USED IN TEXT

acetyl-CoA = acetylcoenzyme A
ADP = adenosine diphosphate
ATP = adenosine triphosphate
FFA = free fatty acids
V_{O_2} max = maximal oxygen uptake

TABLE 1.—*Fuel Reserves in an Average Man**

Fuel	*Tissue*	*Fuel Reserves in an Average Man* *Kcal*	*Grams*
Triglyceride ..	Adipose tissue	100,000	15,000
Glycogen	Liver	200	70
	Muscle	400	120
Glucose	Body fluids	40	20
Protein	Muscle	25,000	6,000

*Reprinted by permission from Newsholme,[34] p 88.

additional four miles. Obviously the large adipose reserve must be mobilized for fuel. Protein is largely, although not entirely,[5] inaccessible as fuel.

Muscle fuels are either endogenous (glycogen and triglyceride) or exogenous (free fatty acids [FFA] and glucose).[6] Endogenous fuels are handled more efficiently because they do not require mobilization or uptake, and are instantly available for energy when the contractile apparatus activates.

The reservoir for blood glucose is hepatic glycogen, which is converted through a series of enzymatic steps to glucose-6-phosphate. This in turn is converted to glucose by the enzyme glucose-6-phosphatase, and delivered into the blood for use by body tissues. Muscle lacks glucose-6-phosphatase. Hence, muscle glycogen can *only* by utilized by the individual muscle fiber in which

TABLE 2.—*Characteristics of Type I and Type II Fibers in Human Skeletal Muscle Studied in Needle-Biopsy Specimens of Quadriceps**

Characteristic	*Type II Fibers*	*Type I Fibers*
Reaction to myosin ATPase stain	Pale staining, low activity	Dark staining, high activity
Morphology and histochemistry		
Fiber size, μ (untrained men)	68.9	69.2
Relative fiber frequency, % (untrained men)	58	42
Capillary, no. of capillary contacts per unit cross-section ($\mu^{-2}10^{-3}$)	1.03	0.85
α-Glycerophosphate dehydrogenase, microphotometry	Lower activity	Higher activity
NADH tetrazolium reductase, microphotometry	Higher activity	Lower activity
Contractility		
Relaxation rate (% force loss per 10 milliseconds)	7.6	15.7
Contraction time (milliseconds to peak twitch)†	102,60,105,102 (4 motor units)	44,62 (2 motor units)
Fatigability†		
Repetitive stimulation	Resistant	Fatigable
Repetitive voluntary contractions	Resistant	Fatigable
Metabolic heat production (cal • $min^{-1}g^{-1}$)	0.35	2.15
Enzyme activity (pooled or individual fibers, freeze dried)		
Mg^{++}ATPase mol • 10^{-4}g • $protein^{-1}min^{-1}$ (24°C)	0.3	0.85
Creatinine phosphokinase mol • 10^{-4}g • $protein^{-1}min^{-1}$ (24°C)	13.1	16.6
Myokinase mol 10^{-4}g • $protein^{-1}min^{-1}$ (24°C)	6.6	12.1
Lactate dehydrogenase (lactate→pyruvate) mol • 10^{-4}g $protein^{-1}min^{-1}$ (24°C)	1.45	3.66
Phosphofructokinase mmol • $kg^{-1}min^{-1}$ (25°C)	25.8	49.4
Succinate dehydrogenase mmol • $kg^{-1}min^{-1}$ (25°C)	29.6	19.3
Energy stores (pooled or individual fibers, freeze dried)		
Glycogen, mmol • kg^{-1}	355	359
Triglyceride, mmol • kg^{-1}	207	74

NADH = nicotinamide adenine dinucleotide

*Source: Edwards R, Young A, Wiles M: Needle biopsy of skeletal muscle in the diagnosis of myopathy and the clinical study of muscle function and repair. N Engl J Med 302:261-271, Jan 31, 1980

†Determined in medial gastrocnemius, peroneus longus.

the glycogen is stored. The glucose-6-phosphate units enter the Embden-Meyerhof pathway for cellular combustion. Similarly, the reservoir for the plasma free fatty acids is the body adipose tissue. Hormonal stimulation of adipose lipase cleaves stored triglyceride into glycerol and three FFA, which are released into the blood. As is the case for muscle glycogen, muscle triglyceride is not exportable, as shown by the inability to show glycerol efflux from working muscle.[7]

Fiber Types

Human skeletal muscle is a mosaic of two fiber types, designated type I and type II on the basis of myofibrillar ATPase activity measured at alkaline pH.[8] Type II fibers (high ATPase activity) are further subdivided into types IIa and IIb (Table 2). The proportion of fiber types is genetically inherited and independent of sex, although variability is greater in males.[9] The average composition of the human quadriceps muscle is 52 percent type I, 33 percent type IIa and 14 percent type IIb.

As shown in Table 2, type I, or slow twitch fibers, are characterized by higher oxidative enzyme activities, greater vascularization, higher myoglobin content and higher lipid stores.[10] These fibers are ideally suited for activity of myofibrillar ATPase and glycolytic enzymes. Type II fibers develop peak tension more rapidly than type I fibers, but fatigue more rapidly, because of their lesser oxidative capabilities. Type IIa fibers have greater oxidative capacity than type IIb fibers.[10]

Glycogen content is the same in both types of muscle fiber. By doing biopsies on muscle after different types of exercise, the degree of glycogen depletion in each of the fiber types gives an indication of which type is used preferentially.[11,12] As expected, type I fibers are utilized for prolonged, aerobic work. Type II fibers are used for high intensity work of short duration. In exercise at marathon intensity (70 percent to 80 percent Vo_2 max) type I fibers are used primarily. Type II fibers are utilized at the initiation of exercise, before vasodilatation and substrate delivery to type I fibers are maximal, and are recruited as exercise is prolonged and type I fibers fatigue. Thus, recruitment of type II fibers is dependent on the intensity and duration of exercise.

As might be expected, an increased proportion of type I fibers would confer a metabolic advantage in an event like the marathon, because of the increased aerobic capacity of the muscle. Several studies have documented positive correlations between Vo_2 max and percent of type I fibers, and between time to fatigue and percent of type II fibers.[13,14] That elite athletes gravitate to events at which they have genetic favorability is substantiated by biopsy data showing a high proportion of type I fibers (up to and over 90 percent) in successful long-distance runners versus the predominance of type II fibers in sprinters.[15]

Training does not change the inherited proportion of fiber types,[16] although there are data that show conversion of type IIb fibers to their more oxidative type IIa profile with endurance training.[17] Training, however, is much more important than genetics in predicting success. Endurance training further increases oxidative capacity by inducing mitochondrial proliferation in the type I fibers,[18] changing type II fibers to a more oxidative profile,[17] enhancing the activity of enzymes which mobilize and transport fatty acids to the muscle,[19-24] and increasing sensitivity to the various hormones which orchestrate the metabolic response.[25] This increased oxidative capacity is reflected by the increased Vo_2 max in elite distance runners. However, fuel utilization characteristics are applicable to all runners of all abilities, and the following comments apply to all runners.

Endogenous Fuels

Triglyceride

Although muscle triglyceride can contribute up to between 50 percent and 70 percent of the total fatty substrate with exercise,[6] the endogenous triglyceride levels in muscle seem not to affect performance. Depletion rates are related to the amount stored, and not to intensity or duration of exercise.[26] In fact, elite runners have lower endogenous muscle lipid levels. The lesser importance of endogenous lipid supply to total fat metabolism may be related to the fact that FFA uptake is not rate-limiting in muscle.[27]

Glycogen

Repeat muscle biopsy specimens obtained during the course of running at a steady intensity to exhaustion show a curvilinear decline in muscle glycogen as exercise is continued. The amount of muscle glycogen decreases from a normal level of 9 to 20 grams per kg of muscle to 0.6 to 1.0 gram per kg (wet weight).[28] With muscle glycogen depletion, exhaustion occurs and the running pace can no longer be sustained. Regardless

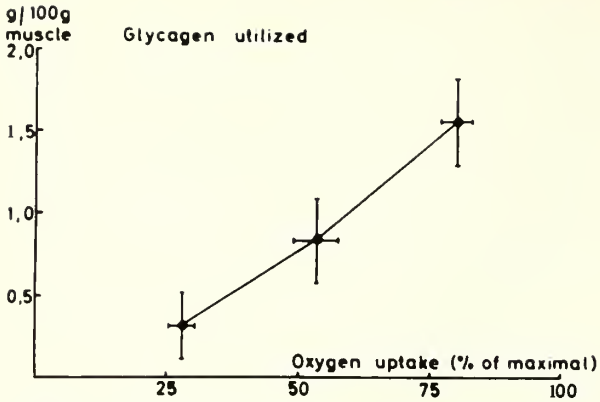

Figure 1.—Decrease of muscle glycogen after one hour of exercise at three different work levels (mean ±SD, n=8). (Reprinted by permission from Hermansen et al,[28] p 129.)

of the pre-exercise glycogen level, fatigue occurs with glycogen depletion.[29] At intensities of 70 percent Vo_2 max, pace cannot be sustained when muscle glycogen content falls below 3 to 5 grams per kg of muscle.[30] No other variable, including blood glucose, lactate, pyruvate, change in heart rate or oxygen consumption, or fall in body weight (with fluid depletion), correlates so consistently with fatigue during sustained aerobic exercise. Glycogen depletion occurs in a characteristic pattern during aerobic exercise of this intensity, first from the aerobic type I fibers and only later from type II fibers as they become recruited.[11]

Two important points about the glycogen depletion pattern deserve emphasis. First, at a given exercise intensity (70 percent to 80 percent Vo_2 max for the marathon), the *pre-exercise glycogen content* of the muscle will determine the *duration* of sustained optimal pace. Second, the shape of the curve shows a disproportionate depletion occurring at the initiation of exercise. Much of this, up to 20 percent of the total glycogen utilized, is consumed in the first five minutes of exercise.[6] This "glycogen burst," perceived by the runner as discomfort before the "second wind" begins, is due to the recruitment of type II glycolytic fibers for anaerobic glycolysis at the beginning of running, before blood flow is redistributed to the working muscles bringing oxygen and substrates for oxidative metabolism. Whether true local hypoxemia or high catecholamine levels (principally epinephrine) at the beginning of the race mediate the glycogen burst is unclear. The glycogen burst is reflected by the rising levels of lactate in blood and muscle at the onset of exercise, which gradually clear as exercise continues.[6,31]

The other critical point about glycogen depletion is that the *rate* of utilization is directly proportional to exercise intensity (percent Vo_2 max), or pace (Figure 1).[28] Whereas fats alone can supply most of the needs for resting muscle, exercising muscle has an *obligate* requirement for carbohydrate substrate, which is met primarily by glycogen, and this obligate requirement increases with intensity of effort.

The reason for this obligate use of glycogen is not entirely clear, but may be related to the following: increasing recruitment of glycolytic type II fibers as pace quickens[11,12]; the greater high-energy phosphate yield per mole of oxygen consumed for carbohydrates (P:O=3.0) in comparison to fats (P:O=2.8 for palmitic acid, the most abundant saturated fatty acid)[32]; the increasing hormonal stimulus to glycogenolysis as intensity increases, principally mediated by increasing catecholamine levels,[33] and the increasing cellular adenosine diphosphate (ADP) to adenosine triphosphate ratio, which favors glycolysis over fatty acid oxidation.[34]

The performance corollary is that increasing intensity (pace) will shift the glycogen depletion curve to the left, and for a given exercise intensity, shorten the duration of sustained effort. The rate of muscle glycogen depletion in the marathon effort (70 percent to 80 percent Vo_2 max) is approximately 0.5 gram per kg of muscle per km.[30]

Realizing that glycogen depletion determines duration of exercise, a simple calculation underscores the marathon runner's dilemma. Assuming a working muscle mass of 20 to 25 kg, and a normal glycogen content of about 18 grams per kg of muscle, the available muscle glycogen will be approximately 400 grams. At the known glycogen depletion rate for marathon pace, 10 to 12.5 grams of glycogen will be used per km as obligate substrate. Therefore, total glycogen depletion will occur between 32 and 40 km (19.8 and 24.8 miles) of a 42 km (26.2 mile) race.

What happens then is known in runner's parlance as "hitting the wall." Although other factors contribute to the "wall" in the marathon, including dehydration and mental fatigue, glycogen stores are the final determinant of exercise duration at this intensity.

It follows from the shape of the glycogen depletion curve that attempts to either shift the curve upwards and to the right, or change the rate of depletion, would enhance endurance.

The influence of diet on exercise performance

was described by Christensen and Hansen in 1939.[35] They showed that subjects ingesting a carbohydrate-rich diet could work substantially longer than those ingesting a protein-fat diet (210 minutes to exhaustion versus 80). More recently, Bergstrom and Hultman explored this relationship using muscle biopsy specimens.[28,36] These investigators exercised subjects to glycogen depletion at 75 percent Vo_2 max, and then fed them either a carbohydrate-poor or a carbohydrate-rich diet for three days. They then re-exercised their subjects.

As seen in Figure 2, duration of work correlated well with the initial glycogen level, as predicted. Surprisingly, a pronounced effect of diet on glycogen storage was documented, with individual subjects storing up to 45 grams per kg of muscle, more than double the normal upper limit. This allowed a doubling of work duration at an intensity of 75 percent Vo_2 max. Note that these data predict that a marathon run in less than 2 hours 30 minutes would be nearly impossible without elevated glycogen stores.

Four important observations have been made regarding this supercompensation in glycogen storage.

- Supercompensation occurs only following exercise-induced glycogen depletion. Carbohydrate-rich diets following a fast or low-carbohydrate diet only replenish muscle stores to normal levels, and over several days.[36]
- If depletion is followed by two to three days of low-carbohydrate diet, and then by a high-carbohydrate diet, glycogen storage is significantly higher.[29]
- Glycogen storage occurs only in those muscles which have been depleted by previous exercise, and only in those fibers which have been depleted. Thus, in experiments studying one-legged exercise to exhaustion, only the depleted (exercised) leg supercompensated after high-carbohydrate feeding.[37] For a depleting run to be effective, it must tax the same muscles and fiber types to be used in the race.
- Finally, fully 60 percent of the total storage occurs in the first 10 hours following high-carbohydrate intake.[38] Normal levels can be reached by 24 hours. Nearly all of the ingested carbohydrate over the first 24 hours is stored in muscle. Hepatic glycogen is also rapidly restored. Muscle loading will continue for three to four days, but increasingly, excess caloric intake will be stored as adipose rather than in carbohydrate deposits.

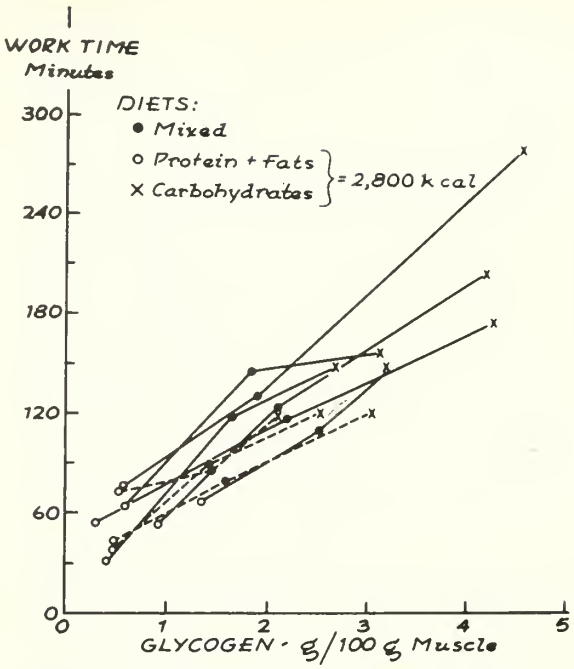

Figure 2.—Relationship between diet, initial glycogen content in quadriceps femoris and work time in nine subjects exercised at the same intensity. (Reprinted permission from Bergstrom & Hultman: JAMA 221:999, 1972[36]; copyright 1978, American Medical Association.)

Frequency of meals may also enhance carbohydrate loading, with improved storage observed with two meals per day versus multiple smaller feedings with the same total caloric value.[39]

The performance aspects of glycogen loading have been documented. Before competing in a 30 km (18.6 mile) race, runners ate either a mixed diet or followed the three-phase glycogen loading protocol, that is, a depleting run, followed by a low-carbohydrate intake for two days and a carbohydrate-rich intake for three days. Three weeks later, the same race was repeated under the same conditions, but all diets were switched. In every case, the glycogen-loaded runner had a faster time. Fatigue and inability to maintain the initial pace occurred near the time that muscle glycogen content fell below 3 to 5 grams per kg of muscle.[30] Of note, glycogen loading did not increase the initial pace for any of the runners, but only the duration for which optimal pace could be sustained.

The reasons for supercompensated storage after exercise are unknown, but may be related to observed affinity changes in the insulin receptor with exercise,[40] starvation[41] and high-carbohydrate feeding.[42] An additional benefit of glycogen loading is the 2.7 grams of water stored intracellularly with each gram of glycogen, and the 0.6 gram of

water formed by the metabolism of 1 gram of glycogen. Thus, each gram of glycogen stored in muscle yields just over 3 grams of water for repleting evaporative losses incurred with exercise.[36]

Exogenous Fuels

Glucose

The blood glucose represents a relatively small caloric source (20 grams) which must be preserved for utilization by the brain, blood cells and anaerobic tissues of the body. With exercise, peripheral uptake of glucose is greatly enhanced, despite the falling insulin levels,[43] a feature appreciated by diabetes specialists years ago. The exercise-induced glucose uptake does require small amounts of insulin, probably less than 10 to 12 mU per ml.[44] As exercise is continued, glucose turnover can increase 10-fold to 15-fold, and by three hours at moderate intensity can account for about a third of the total oxidative metabolism of the leg in human subjects.[45] In trained runners, who display improved FFA mobilization and utilization, less glucose is used, but it may still account for 10 percent to 20 percent of total metabolic needs.

Hepatic glucose output increases progressively up to fivefold as exercise continues, first through glycogenolysis, and later through enhanced gluconeogenesis, as three-carbon substrates (principally alanine, lactate, glycerol and pyruvate) become available.[43,46]

All the major hormonal changes of exercise serve to preserve the blood glucose, and to mobilize stored complex fuels to simpler forms that can be utilized by working muscle. Of major importance are the rise in catecholamines and fall in insulin levels. Thus, epinephrine stimulates glycogenolysis, inhibits insulin release and interferes with insulin action peripherally[47-50] norepinephrine mobilizes FFA from adipose tissue; falling insulin levels minimize peripheral glucose uptake while allowing lipolysis and glycogenolysis, and glucagon levels rise to stimulate splanchnic glucose output in concert with increased epinephrine and falling insulin levels.[51,52]

If liver glycogen is depleted, either through starvation or prolonged exercise, and the intensity of effort is such that the obligate carbohydrate requirement for the working muscle exceeds the glycogen content, blood glucose will be utilized. Gluconeogenesis alone cannot maintain the blood glucose at high work intensities, and hypoglycemia occurs, stopping exercise.[53]

At moderate work levels ingested glucose can be utilized by working muscle, thus sparing muscle glycogen.[54] But at marathon race pace, ingested glucose has little sparing effect on glycogen.[55] This may be due to the increased epinephrine levels at high work loads. In fact, large doses of glucose preceding exercise will raise portal vein insulin levels and substantially lower blood sugar by impairing hepatic glucose output.[56]

Free Fatty Acids

Free fatty acids are the major exogenous substrate for working muscle. They are taken up and oxidized almost to completion in direct relationship to arterial concentration.[7,57] The rate-limiting step in muscle FFA use is in mobilization from adipose stores. The latter occurs principally through norepinephrine stimulation of adipose lipase,[58] which cleaves triglyceride, yielding glycerol and three FFA molecules, which are transported in blood bound to albumin.

At initiation of running, FFA levels decline owing to uptake by working muscle.[59] Subsequent FFA mobilization is rapid, mediated by sympathetic outflow and falling insulin levels. After the initial lag, mobilization outstrips uptake as documented by rising levels of plasma FFA and glycerol. After 40 to 60 minutes of running, FFA levels have risen to six times basal levels. Turnover of FFA rises as well, reflecting increased muscle utilization of fatty substrate as exercise continues, shown by the falling respiratory quotient in exercising subjects. Except for the initial lag period, mobilization continues to supply FFA faster than demand, and fractional extraction of FFA actually decreases as exercise is continued.[60] When exercise stops, mobilizing forces are unmasked as an overshoot in the FFA level, which is responsible for the ketosis after exercise.

The relationship of FFA utilization to exercise intensity (percent Vo_2 max) is the reverse of that for glycogen.[61] Therefore, at rest and with prolonged light exercise, fats can supply over 90 percent of the oxidative needs of the muscle. At moderate work intensities, free fatty acids become the major blood-borne fuel, supplying up to 50 percent of the needs of the muscle.[60] However, as intensity increases above 55 percent to 60 percent Vo_2 max, the amount of fat put to use declines in direct proportion to the amount of obligate carbohydrate substrate required for reasons previously discussed. This reciprocal relationship creates a continuum of fuel utilization from fats (principally

as exogenous FFA) for low-intensity prolonged energy use, to carbohydrate (principally as endogenous glycogen) for high-intensity short-duration use.

At marathon pace (70 percent to 80 percent Vo_2 max), the utilization of carbohydrate relative to fat is approximately 70:30, although it may be closer to 55:45 in trained long-distance runners. Improved fat metabolism in trained runners is due to enhancement of enzymatic and hormonal activities controlling mobilization and metabolism of FFA.[20,21,62]

The relative importance of endogenous glycogen and exogenous FFA in the fuel spectrum has been investigated.[63] At the intensity of the marathon, blocking-FFA mobilization with nicotinic acid does not impair the ability to maintain pace. However, muscle glycogen utilization increases significantly to cover that portion of oxidative metabolism previously supported by beta-oxidation of fatty acids.[64] This allows two conclusions: first, if free fatty acids are unavailable as substrate, glycogen metabolism will accelerate to cover energy needs at no cost to pace; and second, because glycogen is metabolized more quickly, the total *duration* of sustained effort will be less.

However, we have already seen that at this pace glycogen is an obligate substrate, and FFA alone cannot be used to sustain pace because of its less favorable high-energy phosphate to oxygen ratio. If the legs are first glycogen depleted by a 90 percent Vo_2 max effort, subsequent FFA-supported effort can only achieve 60 percent Vo_2 max, and then with a 45 percent reduction in time to exhaustion. If nicotinic acid is now given, so that both glycogen and FFA utilization are blocked, the blood glucose is utilized until hypoglycemia results, and exercise stops in only half the time as compared with the FFA-supported effort.[63]

At the time of glycogen depletion then, pace must slow down to that effort which can be supported by FFA metabolism. Protein is also used increasingly as substrate when glycogen stores are depleted.[65] As previously noted, the decrement in pace occurs when glycogen content drops below 3 to 5 grams per kg of muscle.[30]

The Fat-Carbohydrate Connection

It is evident that FFA spare glycogen as shown by increased glycogen depletion when FFA mobilization is blocked with nicotinic acid. How does FFA spare glycogen metabolism? Understanding this requires a brief look at biochemistry.[34,66,67]

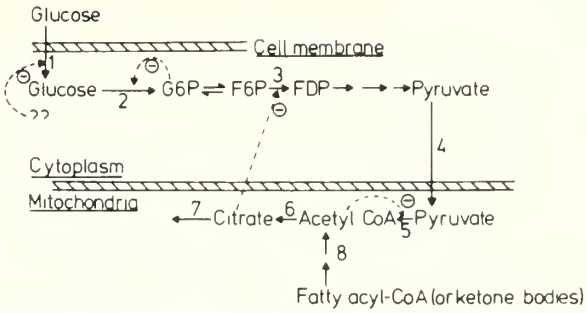

Figure 3.—Mechanism of control of glycolysis by fatty acid oxidation in muscle. The reactions are as follows: (1) membrane transport of glucose; (2) hexokinase; (3) phosphofructokinase; (4) pyruvate transport into the mitochondrion; (5) pyruvate dehydrogenase; (6) citrate synthase; (7) further reactions of the citric acid cycle; and (8) beta-oxidation system (or pathway of ketone body utilization). The dotted lines indicate allosteric regulatory mechanism by which some nonequilibrium reactions of glycolysis are controlled via the rate of fatty acid (and/or ketone body) oxidation in muscle. The allosteric factor regulating glucose transport is unknown. (FDP = fructose-1,6-diphosphate; F6P = fructose-6-phosphate; G6P = glucose-6-phosphate.) (Reprinted by permission from Newsholme,[34] p 81.)

Figure 3 illustrates cellular metabolism, including the glycolytic pathway by which glucose in the cytoplasm is metabolized to pyruvate, which then crosses into the mitochondria to enter the citric acid cycle. Fatty acid uptake and transport in muscle cells are not rate-limiting, as we have seen. Fatty acids are always available in excess with exercise, and they will be metabolized to introduce acetyl-CoA (acetylcoenzyme A) to the cycle. The increase in the acetyl-CoA to CoA ratio inhibits pyruvate dehydrogenase by converting it to its inactive form. Furthermore, rising citrate levels inhibit phosphofructokinase (PFKase). Fructose-6-phosphate levels build up in the cell causing glucose-6-phosphate levels to rise, and inhibit hexokinase. Thus, the glycolytic pathway is slowed at several steps when fatty substrates are available. Furthermore, FFA have a direct depressant action on membrane glucose transport through unknown mechanisms.

As previously described, however, increasing intensity of exercise obligates glycogen breakdown regardless of FFA levels. As pace increases, the ATP to ADP ratio in the cell falls, as ATP is degraded more rapidly by the contractile proteins (Figure 4). Creatine phosphate levels fall as high-energy phosphate is transferred to ADP. A small decrease in the ATP to ADP ratio causes large increases in several metabolites, including adenosine monophosphate (AMP), inorganic phosphate and

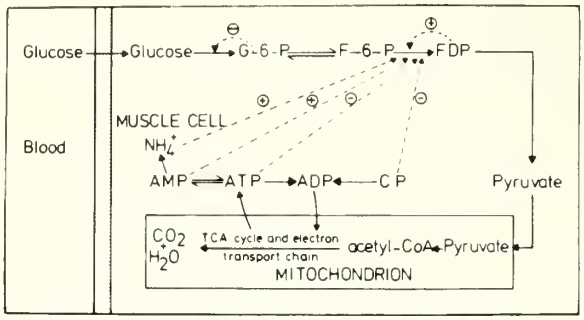

Figure 4.—Regulation of glycolysis in muscle at the glucose transport, hexokinase and phosphofructokinase reactions. (ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; CP = creatine phosphate; FDP = fructose-1,6-diphosphate; F6P = fructose-6-phosphate; G6P = glucose-6-phosphate; TCA = tricarboxylic acid.) (Reprinted by permission from Newsholme,[31] p 81.)

ammonium ion. These regulator molecules all feedback on PFKase to relieve the citrate block and accelerate glycolysis. Furthermore, pyruvate will be preferentially utilized over fatty acetyl-CoA at entry into the electron transport chain as the ADP concentration rises. Therefore, the ratio of ATP to ADP, which reflects the *intensity* of effort, or pace, precisely determines the ratio of carbohydrate to fat metabolism. At lower intensities, fat metabolism spares glycogen, but as intensity increases, more efficient high-energy phosphate generation is required, and fat metabolism is replaced by glycogen.

Thus, we have seen that (1) free fatty acids are mobilized more rapidly than they are metabolized by the working muscle—this accounts for the rising FFA levels as exercise continues; (2) FFA uptake and utilization are not rate-limiting, and (3) the pace, by determining the cellular ATP to ADP ratio, will determine to what extent FFA can be used to spare glycogen. Therefore, with exercise, FFA are always available in excess of the needs of the working muscle, and raising levels further would not be expected to enhance performance.

There is only one point during exercise when FFA availability to muscle may not be optimal. This occurs at the beginning of exercise, when FFA levels fall slightly while mobilizing mechanisms lag behind muscle uptake. This occurs at the same time as the glycogen burst, and because FFA spares glycogen breakdown, it follows that raising the FFA levels at the onset of exercise may spare glycogen for later use. Because the glycogen burst can consume up to 20 percent of the total glycogen stored, this may make a significant contribution to performance.

In rats given a fatty meal and heparin to maximize FFA levels, and then run on a treadmill for 30 minutes, glycogen depletion was substantially less than in control animals. Both skeletal muscle (type I fibers) and hepatic glycogen were spared, with total glycogen depletion decreased by 40 percent. Increased citrate levels were observed in both muscle and liver, consistent with increased FAA metabolism.[68] As predicted, time to exhaustion was consistently prolonged in the animals with initially elevated FFA.[69]

Results were similar in human subjects given a fatty meal five hours before exercise and heparin intravenously just before a 70 percent Vo_2 max, 30-minute treadmill run.[70] Muscle biopsy specimens showed a 40 percent decrease in glycogen consumption. Total carbohydrate consumption decreased 17 percent and fat consumption rose 32 percent more than in controls. Blood glucose levels were higher also, presumably reflecting FFA inhibition of glucose uptake by muscle.

Caffeine will also raise FFA levels through its phosphodiesterase and catecholamine-releasing activity.[71] Runners were given 330 mg of caffeine or placebo orally in a single-blind study, 60 minutes before an 80 percent Vo_2 max run to exhaustion. In all runners, caffeine increased time to exhaustion by an average of 19.5 percent, from 75 to 90 minutes.[72] The total carbohydrate consumed (240 grams) was identical with and without caffeine as expected, but fat metabolism rose from 57 to 118 grams after caffeine. This permits glycogen spared from the original glycogen burst to be utilized later, thereby increasing duration of exercise.

Summary and Conclusions

The following data summarize studies of fuel metabolism as applied to the marathon.

- The pre-exercise muscle glycogen content determines the duration of performance.
- There is obligate glycogen utilization at the pace of a competitive marathon, approaching 0.5 gram per kg of muscle per km.
- When muscle glycogen falls below 3 to 5 grams per kg of muscle, pace must decrease, as effort is sustained by fat metabolism.
- The glycogen burst at the initiation of exer-

cise contributes a significant portion (approximately 20 percent) of total glycogen utilization.

- Dietary manipulation can double muscle glycogen levels.
- Free fatty acids spare glycogen to that required for the obligate carbohydrate substrate as determined by the ATP to ADP ratio (pace).
- The rate-limiting step in FFA metabolism is mobilization from adipose tissue.
- Mobilization lags behind utilization only at the onset of exercise, coincident with the glycogen burst. Otherwise, FFA are available in excess of need.
- Raising levels of FFA at the onset of exercise can substantially spare glycogen that would otherwise be consumed in the glycogen burst and, hence, enhance performance.

In practical terms, the following guidelines should be useful to marathon athletes.

- Optimal glycogen loading involves the three phases of depletion (exercise), a carbohydrate-poor diet followed by a carbohydrate-rich diet. Depletion exercise must use the same muscles as will be used in the race. A carbohydrate-poor diet for two days will optimize subsequent glycogen storage. A carbohydrate-rich (greater than 70 percent carbohydrate) diet should be consumed for three days before competition, with only light training, to preserve muscle glycogen stores. The runner should maximize caloric intake (as carbohydrates) for the first 10 to 24 hours of carbohydrate loading, and then eat only isocaloric, high-carbohydrate diet for the remaining 2 to 2½ days before competition. This takes advantage of the high specific storage immediately after depletion, and minimizes storage in adipose tissue, with its potentially disadvantageous weight gain.[73] Two meals per day may achieve higher glycogen levels than many small feedings.
- The last sugar intake should be four to six hours before competition to assure high hepatic glycogen stores while allowing insulin levels to decrease to postabsorptive levels; 100 grams of carbohydrate (two candy bars) is adequate.
- Caffeine (5 mg per kg of body weight; one NoDoz tablet contains 100 mg of caffeine) taken orally an hour before competition will raise FFA levels and spare glycogen that would otherwise be consumed in the glycogen burst at the beginning of the race.

Although these metabolic considerations can benefit runners at any level of ability, it is important to realize that metabolic manipulations can in no way approach the beneficial effects of consistent training on performance.

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Important Advances in Clinical Medicine

Epitomes of Progress — General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in general surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Portal Hypertension

THE DIAGNOSIS of hemorrhage from esophageal varices can only be made with certainty after other sites of hemorrhage have been excluded by endoscopy. Alcoholic patients have an increased incidence of gastritis, duodenal ulcer and Mallory-Weiss tear of the esophagus. Indeed, up to 30 percent of patients with documented esophageal varices who present with upper gastrointestinal hemorrhage are bleeding from a site other than their varices. Endoscopy frequently establishes varices as the origin of hemorrhage. If esophageal varices are present but not bleeding, they are nevertheless assumed to be the source of hemorrhage if other bleeding sites are excluded by endoscopic examination.

Although some enthusiasm persists for emergency portacaval shunts within eight hours of admission, most American surgeons attempt nonoperative arrest of hemorrhage by intravenous administration of vasopressin (Pitressin) or balloon tamponade (or both), interventions that control variceal hemorrhage in 80 percent to 90 percent of patients and make it possible for elective operation to follow. If forced to carry out an emergency shunt, we prefer the end-to-side portacaval shunt, although the mesocaval interposition shunt is favored by many. Because substantiation of the claims of technical simplicity or maintenance of hepatopedal flow with the mesocaval shunt are unproved, the high thrombosis rate of the mesocaval shunt makes it a second choice to the end-to-side portacaval shunt.

For elective shunts, the Warren distal splenorenal shunt is preferred over conventional portasystemic shunts, because of its lower incidence of postoperative encephalopathy. Moreover, with the Warren shunt, unlike conventional shunts, prolongation of life (in nonalcoholic cirrhotic patients and perhaps in alcoholic patients who stop drinking) has been reported. The Warren shunt is too technically challenging for emergency situations. The presence of significant ascites is a contraindication to a Warren shunt, and for patients with poorly controlled ascites, a side-to-side variety of shunt is preferred.

Two recently described techniques for direct control of the bleeding from esophageal varices are the extensive gastroesophageal devascularization of Sugiura (of Japan) and simple esophageal transection with a stapler. Although the role of these procedures is as yet unclear, the Sugiura procedure has failed to be as useful in American cirrhotic patients as expected. It is likely that esophageal transection procedures will be associated with a high rebleeding rate.

A common clinical dilemma occurs in patients with poor liver function (Child's C classification), who continue to bleed from varices in spite of

conservative measures. An emergency portacaval shunt in patients with Child's C classification will have an operative mortality in excess of 50 percent. Because of the unacceptably high operative mortality of patients with Child's C classification, endoscopic sclerotherapy is being evaluated as an alternative to operation.

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The Diagnosis of Jaundice

CLINICAL PRESENTATION, physical examination and biochemical findings frequently will provide sufficient information to establish a diagnosis in many patients who have jaundice. In a significant percentage of these patients, however, one or more of the newer radiological or nuclear medicine techniques will be necessary to differentiate between extrahepatic obstruction and hepatocellular disease. The noninvasive tests that have recently been employed in the diagnosis of jaundice include gray-scale ultrasound (GSU), computerized tomography (CT) and scanning of the biliary tract (scintigraphy) with various hepatobiliary agents labeled with technetium 99m. In addition, transhepatic cholangiography (THC) with the thin-needle (Chiba) technique and endoscopic retrograde cholangiography (ERC) have also been evaluated in jaundiced patients.

Ultrasound has been reported to have an overall accuracy as high as 95 percent in differentiating dilated from nondilated ducts although some series report only 50 percent to 75 percent sensitivity for GSU's ability to detect duct dilatation. In comparison, CT has uniformly been reported to make this differentiation in more than 90 percent of jaundiced patients. A third noninvasive technique, biliary scanning, has also been shown to be very accurate in detecting complete bile duct obstruction. The ability of scintigraphy, however, to diagnose accurately patients with hepatocellular disease or partial duct obstruction has been reported to be only 88 percent and 81 percent, respectively.

Unfortunately, the ability of each of these noninvasive tests to consistently provide useful information about the exact cause and precise location of an obstructing lesion is limited, and the information provided by each of these tests may be no more accurate than a careful clinical assessment. By comparison, THC with Chiba needle is successful in opacifying dilated ducts in almost all cases. If failure to visualize the biliary tree is considered as evidence of hepatocellular disease, THC is able to differentiate medical from surgical jaundice with nearly 100 percent accuracy.

ERC has also been shown to be highly accurate in establishing the cause of jaundice. Both THC and ERC have the advantage of providing exact anatomic details; and although these procedures are invasive, they can be done with an acceptably low incidence of complications. Of these two procedures THC has the advantages of lower cost, wider availability and a high probability of success in patients with obstructed ducts. On the other hand, ERC should be employed in patients with coagulation defects, when THC has failed, or when duodenoscopy or pancreatography is likely to provide useful information.

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Transluminal Dilatation

TRANSLUMINAL DILATATION was introduced by Dotter in 1964. It has since gained wide acceptance in Europe and gradually increasing acceptance in the United States. The technique consists of passing a guide wire under fluoroscopic guidance through stenotic or occluded segments of atherosclerotic arteries and then advancing a catheter with a balloon attached to it over the guide wire. The balloon is then inflated in the diseased segment so as to dilate the artery. The balloons are designed in such a way that a given amount of pressure—for example, five atmospheres for many balloons—will inflate the balloon to a predetermined size. The newer balloons are designed so that even if more than the recommended pressure is applied the balloons will still not expand much beyond their stated size.

Transluminal dilatation has several attractive features. It requires only local anesthesia. No prosthetic material need be implanted. Collateral blood flow is either maintained or improved with

dilatation and surgical procedures can be used later if the dilatation fails.

The disadvantages of transluminal dilatation are also several: Passage of the guide wire can lift intimal flaps which then cause occlusion. The guide wire can perforate the arterial wall. The balloon can become impaled on an intimal flap. Fragments of a fractured atherosclerotic plaque can embolize distally. And, finally, long-term results with transluminal dilatation in this country are still unknown.

Nonetheless, the incidence of complications is low enough so that transluminal dilatation may be offered to patients who are poor surgical candidates or, on a trial basis, to any patient who has a lesion that is short and appears favorable for dilatation. Dilatation of superficial femoral and iliac artery lesions has given good long-term results. Dilatation of renal artery lesions has given good short-term results with long-term results still unknown.

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Coronary Heart Operations

SURGICAL MANAGEMENT is recommended for selected patients with coronary heart disease who have myocardial ischemia, mechanical complications of acute myocardial infarction, or medically intractable, symptomatic, ventricular tachyarrhythmias.

Coronary artery bypass is a physiologically effective means of increasing myocardial blood flow. This procedure is applied to patients with significant obstruction (75 percent or greater cross-sectional area) of one or more major coronary arteries who meet clinical or laboratory criteria for important myocardial ischemia. Prime surgical candidates are patients whose anginal symptoms are difficult to control medically or who, on noninvasive testing (exercise electrocardiography or thallium scintigraphy), have myocardial ischemia at low exercise levels. Because survival in ischemic heart disease is inversely related to the extent of coronary atherosclerosis and because it has been shown that patients with extensive coronary artery obstruction live longer when managed surgically, an operation should be considered in such patients even when symptoms are moderately well controlled.

Mechanical complications of myocardial infarction include mitral valvular regurgitation, ventricular septal rupture, ventricular wall rupture and left ventricular aneurysm. These commonly result in severe circulatory compromise and are treated by mitral valve replacement, closure of ventricular septal defect, infarctectomy and aneurysmectomy, respectively. When cardiogenic shock is present circulatory support with intra-aortic balloon pumping is a beneficial adjunct to these procedures.

A promising new development is the surgical management of patients with ventricular tachycardia secondary to previous myocardial infarction. Recent studies suggest that intraoperative epicardial and endocardial mapping using multiple electrode probes is effective in precise localization of arrhythmogenic foci. Patients with symptomatic, medically refractory, ventricular tachyarrhythmias may benefit from surgical excision of these foci. It has been shown that the area of delayed conduction thought to be critical for reentrant ventricular tachycardia can be localized in the border between the aneurysm and normal muscle. These areas are not usually removed with standard aneurysmectomy. Intraoperative localization followed by subendocardial resection combined with aneurysmectomy appears to provide better antiarrhythmic management than aneurysmectomy alone.

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Amputation

THE LATEST ADVANCE in lower extremity amputation for arterial occlusive disease is the concept of a team approach for optimum patient management. The team consists of a surgeon, radiologist, prosthetist, physical therapist and social worker. The surgeon initially evaluates the patient and develops a data base indicative of the patient's overall health status. In addition, the surgeon will evaluate the extent of the ischemic process

in the extremity so as to make a decision whether or not the ischemia can be reversed by vascular reconstruction or if the level of amputation might by lowered with an improvement of blood supply.

If limb salvage or preservation of limb length is feasible, detailed angiographic visualization of the aorto-femoral-tibial system will be carried out by the radiologist in order to ascertain operability of the diseased vasculature. If the process is irreversible, or if the extent of the vascular occlusive problem is not reasonably operable, precise amputation level selection can be established by using skin blood flow measurements with isotope clearance techniques. Xenon Xe 133 is injected into the skin of the extremity at the most distal site that would encompass the gangrenous or infected process and blood flow is measured in order to ascertain whether or not there is sufficient circulation to permit skin wound healing. Should the blood flow be inadequate, the next higher anatomic site would be sampled. Once the most distal anatomic amputation level, possessing adequate skin blood flow, has been identified, the amputation is carried out by the vascular or orthopedic surgeon in a meticulous manner that recognizes the importance of atraumatic handling of poorly vascularized skin in a patient with arterial occlusive disease.

Following completion of the amputation, a prosthetist, skilled in the techniques of immediate postoperative fitting, enters the operating room and applies a rigid plaster dressing to the extremity. A prosthetic device is incorporated into the cast. The morning following operation, the patient is begun on limited weight bearing and ambulation under the supervision of a physical therapist.

The author's experience with this approach at the Veterans Administration Medical Center in San Francisco and at the University of Arizona, Tucson, has shown that mortality for below-knee amputation could be lowered from 16 percent to 0 percent, failure of healing due to ischemia could be virtually eliminated, and the likelihood of ambulation on a prosthetic device, providing the knee joint was spared, could be virtually assured in all patients who were able to walk before the necessity for amputation. This approach has resulted in a reduced hospital stay without compromise of rehabilitation because the patient can be discharged able to walk following the first cast change, approximately ten days following amputation. With a reduced hospital stay the technique is remarkably cost-effective and the ability to achieve the primary goal of amputation, rehabilitation using a permanent prosthesis, becomes routine. This team approach is now being employed with enthusiasm at the Center for Health Sciences and the affiliated hospitals of the University of California, Los Angeles.

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The Surgical Treatment of Obesity

THE PREVALENCE of morbid obesity, the limitations of nonoperative treatment and patient demand for effective therapy stimulate continuing attempts by surgeons to devise safe and effective procedures to accomplish sustained weight loss. Jejunoileal (JI) bypass accomplishes more reliable and permanent weight loss than any form of nonoperative treatment. Thus, early patient satisfaction is high (above 80 percent) despite the occurrence of life-threatening complications. A pattern of late (beyond five years) complications has emerged including oxalate nephrolithiasis (as high as 43 percent), migratory polyarthritis (5 percent to 10 percent) and bypass enteropathy consisting of abdominal pain and distention, increasing diarrhea and flatus (up to 50 percent). Other complications have appeared beyond five years including cirrhosis of the liver and bone demineralization. JI bypass is still recommended by some surgeons for selected patients with hyperlipidemia but the number of JI bypasses done has diminished notably and reconstitution has been increasingly frequent.

Gastric procedures for morbid obesity involve creation of a small proximal gastric pouch and either a gastrojejunostomy (gastric bypass) or creation of a stoma from the pouch to the remainder of the stomach (gastroplasty). The gastric procedures offer a lower incidence of late complications, and in limited comparative studies have produced early weight loss comparable to JI bypass. Dissatisfaction with the long-term weight loss has led Mason and colleagues to a series of refinements of technique. At a recent bariatric surgery workshop at the University of Iowa three

technical modifications of gastric bypass and 11 modifications of gastroplasty were presented. It was agreed that the gastric reservoir must be small (30 to 50 ml), and the opening to the jejunum or body of the stomach must be no greater than 8 to 12 mm in diameter. Roux-en-Y gastrojejunostomy is preferred for gastric bypass. The use of gastric staples must be reinforced with a second application or sutures. The stoma in gastroplasty may dilate and a variety of techniques to prevent this are being evaluated. The associated complications include operative mortality (0 percent to 10 percent), failure of weight loss (20 percent to 30 percent), stomal obstruction (0 percent to 10 percent) and stomal ulceration (1 percent). Further follow-up will be necessary to determine the ultimate role of gastric procedures for relief of morbid obesity.

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Initial Circulatory Support: Fluid Management

SUCCESSFUL TREATMENT depends on rapidly gaining major access to the vascular space by the insertion of one or more venous catheters. The number of catheters will depend on the severity of shock. A cutdown on the long saphenous vein at the ankle is the surest and quickest way to gain access. A cutdown on the basilic vein in the antecubital space is also desirable so that central venous pressure monitoring can be achieved.

In these circumstances the primary goal is to restore adequate plasma volume. During the first 24 hours, it is advisable to use primarily balanced salt solution and whole blood. In mild or moderate shock, it makes little difference what type of intravenous fluid is used—balanced salt solution, normal saline, plasma or plasma products. Cost and availability may be the prime factors in determining which is preferable. However, in severe shock, the type of fluid used is important. This statement is based on the premise that in severe shock (particularly sepsis), endothelial permeability may be increased. Thus, if the endothelium is altered by the shock insult, a "capillary leak" occurs, and the type of fluid to be administered should be based on physiologic principles (Starling's forces).

In the treatment of hemorrhagic shock, the initial resuscitation with crystalloids is favored because the solutions are readily available, effectively restoring vascular volume for short periods and lowering blood viscosity while enhancing resuscitation of the microcirculation. Time is thereby gained for definitive typing and cross-matching of blood, and if the patient continues to bleed during the period of resuscitation, the infused crystalloid solution is expendable (that is, blood bank reserves are not wasted and are available for restoration of blood volume after bleeding has been controlled). Provided the oxygen-carrying capacity of the blood is supplemented by increased oxygen in the airway, it is almost impossible to dilute the blood sufficiently to prevent adequate tissue oxygenation.

The colloids used to treat hypovolemic shock consist of blood, plasma, serum albumin and plasma substitutes such as dextran. Although type O Rh-negative blood was at one time routinely used for resuscitation, major hemorrhage requires massive transfusion; the minor mismatch that often results from transfusion of type O Rh-negative blood may thus be magnified and result in serious morbidity or even fatal reactions. Consequently, type-specific blood should be used, even if it is not cross-matched. When possible, it is preferable to treat with crystalloid solutions while awaiting complete cross-match.

Plasma fractions, including albumin and albumin-containing solutions (Plasmanate), are contraindicated during resuscitation of deep sustained hypovolemic shock. Because of alteration in endothelial permeability or microvascular forces, particles below a molecular weight of 240,000 will leak into the interstitial space, thus increasing tissue oncotic pressure. These interstitial proteins must be mobilized by tissue lymphatics, a process that may take as long as one or two weeks. This prolonged interstitial edema may be deleterious in such organs as the lungs and brain. In contrast, the interstitial edema that results from crystalloid administration is transitory because the fluid is mobilized back into the vascular space and excreted by the kidneys, usually on the second or third day after shock.

Dextran is the most widely used plasma substitute at present. Two types are available: clinical dextran, with a molecular weight of 70,000, and low molecular weight dextran, with a molecular weight of 40,000. Clinical dextran is the most effective colloid because it stays in the vacular system for up to 24 hours. Its disadvantage in

hemorrhagic shock is that it interferes with blood typing and may impair the coagulation and immune mechanism. Low molecular weight dextran (LMWD) is a relatively short-acting colloid, staying in the vascular system approximately eight hours. It interferes much less with blood typing and does not usually depress the coagulation mechanism in dosages of less than 1.5 grams per kg of body weight per 24 hours. Above this amount, LMWD decreases platelet adhesiveness, reducing hemostasis.

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Colostomy

A COLOSTOMY is a stoma created in the colon with the intent to divert the fecal stream from the distal bowel. A colostomy may be prophylactic, as when it is made in the transverse colon to protect a tenuous anastomosis in the rectal segment. The colostomy is maintained until the anastomosis is secure at which time it is closed. Such colostomies are easily made by bringing a loop of colon up above the skin and passing a rod through the mesentery to hold the bowel on the abdominal wall. The loop colostomy does not completely divert bowel contents and therefore is more suitable in the cleansed and decompressed colon. A delayed loop colostomy is a rapid and safe expedient to decompress the obstructed colon, as the stoma is made after the peritoneal cavity has had time to seal about the raised loop of colon, generally 24 hours.

A therapeutic colostomy on the other hand is intended to more completely and permanently divert the fecal stream. The bowel is divided, as distal as possible, to allow for a formed and therefore more manageable excreta. The proximal end is brought out through the abdominal wall in a separate incision (end colostomy). The distal stoma (mucous fistula) may be brought out through the lower pole of the major incision. Therapeutic colostomies are commonly done in conjunction with resection of diseased colon where a primary anastomosis is not feasible or is hazardous. The end sigmoid colostomy made as part of an abdominal perineal resection is an example.

Loop colostomies in the ascending and transverse colon are difficult to manage over extended periods because the fecal material tends to be liquid or semisolid, foul smelling and both copious and continuous. Maintaining a sealed collecting appliance over the stoma is difficult, and leakage and soiling are common. Distal-end colostomies, in contrast, are easily managed with an appliance or may be irrigated once or twice daily and do not require the use of an appliance.

Construction of a colostomy while conceptually easy is technically demanding, particularly in the obese. The mortality in patients receiving a colostomy is high (15 percent to 25 percent) primarily as a result of the underlying disease. Complications such as retraction, prolapse, necrosis and hernia about the site occur in one of every five patients and in 5 percent to 10 percent of these patients reoperation will be required. Wound infections are common. Closure of the colostomy has a mortality of about 1 percent and significant leaks of the closure occur in approximately 5 percent of patients.

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Burn Management

SIGNIFICANT IMPROVEMENTS in the care of patients with burns have been made recently resulting in a substantial decrease in mortality and morbidity. Aggressive fluid resuscitation with a balanced salt solution remains a key to improved early survival. The ideal salt solution remains undetermined. Ringer's lactate or hypertonic lactated saline are both used with success. Colloid is a useful adjunct, best used about 18 hours after the burn. Better understanding of the metabolic effects of a burn have resulted in the use of aggressive nutritional therapy primarily by the enteral route. This has resulted in a measurable decrease in the rate of sepsis and a reversal of the postburn immune deficieney state.

Another advance in the prevention of sepsis has been a more aggressive debridement of the burn wound either by early excision to fascia in the full thickness burn or tangential excision for partial thickness injury with early grafting. This aggressive approach has yielded good results in young patients. However, it appears to be contraindicated in the elderly or those patients with superimposed respiratory damage. The use of

biological dressings as a temporary skin cover has also resulted in improved survival rates in large burns where donor sites are limited. Cadaver skin is the best temporary cover. However, pigskin is also very useful. Early diagnosis and treatment of smoke inhalation with vigorous pulmonary care and ventilatory support has substantially decreased the mortality from this disorder. Bronchoscopy is a very useful diagnostic tool for making that early diagnosis. Steroids have not been found to be useful in this injury. Current areas of progress include improved artificial temporary skin covers and new means of pharmacologically manipulating the burn wound, as well as better understanding and control of burn-induced immune deficiency and hypermetabolism.

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Modern Era of Kidney Transplantation

ALTHOUGH THE 25th anniversary of kidney transplantation has just been observed in Boston, a modern period of rapid development is anticipated. New methods of immunosuppression, tissue-typing (mainly DR matching), coupled with international cooperation of transplantation centers are areas in rapid evolution.

Matching for DR Locus

Persijn and co-workers reported 80 percent cadaver graft survival at six months with zero DR mismatches compared with 67 percent with two DR mismatches. Ting and Morris had 100 percent graft survival at three months with two DR matches, 80 percent at three months with one DR matching and 68 percent with zero DR matching. Terasaki's group reported 100 percent cadaver graft survival at three months with two DR matches compared with 53 percent with zero DR matches. It is important to note that the numbers of full DR-matched patients were extremely small in all of these groups. Albrechtson's claim was more modest when he noted 65 percent one-year cadaveric graft survival in two DR-matched groups compared with 22 percent one-year survival in zero DR-matched recipients.

New Drug—Cyclosporin A

Recently, a fungal metabolite—cyclosporin A—has excited interest as a possible unique addition to the armamentarium of immunosuppressive drugs. It inhibits humoral immunity as shown by reduction of plaque-forming cells in mice. It also suppresses cell-mediated immunity as seen by its effectiveness in preventing graft versus host disease. Morris's group has shown its effectiveness in dog renal allografts and found no hepatotoxicity or nephrotoxicity. They suggested that the drug does not produce clonal deletion of the lymphocytes but merely their suppression. Calne reported its use in 54 patients where it was given initially as the only immunosuppressive agent. There were 12 deaths (22 percent). Besides this high mortality, the side effects were impaired renal function and liver dysfunction. Increased incidence of viral infections and malignancy have also been reported. Starzl commented that mortality in his own series is quite low, because he used cyclosporin in addition to steroids.

Anti-idiotype Antibodies

The production of autoantibodies against clones of antigen-reactive cells reactive to donor histocompatibility antigens producing specific self-unresponsiveness is an important concept in transplant immunology. There is increasing evidence that immunologic unresponsiveness can be induced by either suppressor T-cells or antibodies directed against the T-cell receptor, that is, anti-idiotypic antibodies. The term anti-idiotype has been used to describe the T-cell antigen binding site. This immunization protocol would lead to specific unresponsiveness against relevant alloantigens while leaving the third-party cell intact. The feasibility of inducing specific tolerance of the host towards donor transplantation antigens by autoimmunization has far-reaching clinical implications and this must be pursued further.

Total Lymphoid Irradiation

Samuel Strober, MD, of Stanford University has reported an entirely different method of increasing allograft survival: use of total lymphoid irradiation (TLI). He noted long-term depression of immune function in patients with Hodgkin disease treated with fractionated doses of TLI. They also observed that heart transplants in mice and monkeys were prolonged with TLI. But in dogs the result was not reproducible, only 50 percent of the allografts survived. Grafts versus host disease was not seen in their experiments. Najarian has used TLI only in patients receiving third grafts, for a total dose of 3,250 rad, 125 rad per day for five days per week. All these patients also

received standard immunosuppressive drugs. None of their kidneys were rejected. However, the number is small and the follow-up period is too short. Most feel concerned about increased incidence of neoplasms in these patients, especially of the lymphoma group. TLI totally eliminates lymphocytes also affecting the host suppressor cells, therefore the results may not be reproducible in humans.

Monoclonal Antibodies

Antithymocyte globulin raised against human T-cells in horses and in rabbits has been used in transplant patients since Woodruff reported its usefulness in animal experiments as early as 1963. Because the T-cell population consists of a number of subclasses, it is not surprising that the immunization of an animal with human lymphoid cells results in a multispecific response. With the use of cell hybridization techniques, a number of monoclonal antibodies with specific reactivity to human T-cell subclasses has now been prepared. Monoclonal antibodies raised against T-cytotoxic cells, T-helper cells and B-cells may be used in clinical practice in the near future.

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Blood Transfusion

MANY NEW TRENDS and practices have evolved in hemotherapy. Modern hemotherapy is based on the assumption that administered blood products are targeted to an identified hematologic defect. Component therapy has rapidly become standard practice; two thirds of dispensed blood products are now in the form of components, rather than whole blood in many areas.

The liquid preservative of choice in most blood banks is now citrate-phosphate-dextrose (CPD). CPD-adenine, a citrate preservative with added purine nucleotide, is now licensed, and allows extension of shelf-life of liquid preserved blood from 21 days (CPD) to 35 days (CPD-adenine). The major advantage of both preservatives—over the older preservative, acid-citrate-dextrose (ACD)—is superior preservation of 2,3 diphosphoglycerate (2,3 DPG), the major mammalian organic phosphate which regulates the affinity of hemoglobin for oxygen.

The Standards Committee of the American Association of Blood Banks has recommended that hemolysin testing for ABO antibodies in plasma be discontinued. The effect of this judgment is that universal donor O-negative blood with low plasma titers to A and B antibodies is no longer available and red cell concentrates, washed before transfusion, are the preferred transfusion unit, to insure minimal recipient sensitization.

Blood substitutes, an area of research that has been of greater interest in Japan, Europe and the Soviet Union than in the United States, have received renewed interest. Although gradual improvement in oxygen transport characteristics and safety of stroma-free hemoglobin has occurred, it has yet to become available to patients. Perfluorochemicals, however, have been recently used in Jehovah's Witnesses, in lieu of blood transfusion. Although perfluorochemicals remain an experimental drug requiring an investigative new drug (IND) permit, selected approval for use has been granted by the Food and Drug Administration. The problems associated with the development of perfluorochemicals relate to the need to keep current preparations frozen to maintain stability, slow excretion of current perfluorochemicals from the body, efficacy and lack of information about long-term effects. It remains to be determined if this family of chemicals has a role in hemotherapy.

A significant continued category of problems affecting hemotherapy surrounds the availability and procurement of blood products and governmental regulations. The American Blood Commission, founded to unify agencies procuring and dispensing blood, and to develop a national blood policy, has yet to secure agreement between the major organizations—the American Red Cross and the American Association of Blood Banks—as to donor policy. Hearings have been held on the Blood Assurance Act of 1979, sponsored by Senator Richard S. Schweiker. The controversy continues to focus on whether credits should be allowed for donors for future use, and the appropriateness of a replacement deposit fee. The effect of disallowing recruitment incentives by legislation is unknown, as to the potential impact on total blood supply locally or nationally. A recent law suit in California by the State Department of Consumer Affairs against the Irwin Memorial Blood Bank of the San Francisco Medical Society concluded with the nonreplacement fee remaining blood bank policy.

Because of the demands on available blood resources and the minimal priority that the lay public places on blood donation, surgeons must assume increasing responsibility for encouraging patients and families to provide blood donations. Through hospital transfusion committees, implementation of maximal surgical blood order schedules should become standard practice to more efficiently utilize this precious resource.

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Recent Developments in Trauma Management: The Ruptured Spleen

ONE OF THE new concepts in trauma which remains controversial pertains to the management of the ruptured spleen. It is now recognized that a patient after splenectomy has an increased risk for infectious complications. This is well established in the pediatric age group where lack of humoral immunity renders a child after splenectomy vulnerable to virulent infections, particularly those related to the encapsulated organisms—pneumococci and meningococci.

There also is a peculiar vulnerability in adults—especially to acute postoperative infections. The risk of infection following trauma to the spleen with splenectomy is ten times that of corresponding injuries to the liver (5.0 percent versus 0.5 percent).

These observations have led surgeons to attempt to save ruptured spleens. Overenthusiasm in saving spleens that are badly traumatized has in turn led to immediate bleeding complications. These hemorrhagic complications may pose greater immediate threat to a patient than infection. Despite papers to the contrary, hemoperitoneum requires operative diagnosis. Transfusion in quantity, based on the assumption that a ruptured spleen is present, and if present, will cease to bleed, is inappropriate.

At present it appears that in children under 10 years of age it is appropriate to carry to some length the attempt to salvage all or a portion of the spleen. In young adults, it is appropriate to try to save spleens that are grossly intact in which there is no hilar injury, whereas in adults over the age of 40 years and patients with associated major injuries the spleen should not be saved unless the injury is minimal.

Based on our experience, it is our estimate that 50 percent of spleens in children can be salvaged, 20 percent to 30 percent of those of young adults, and 10 percent to 20 percent of older adults. However, if the surgeon is inexperienced in trauma management, conservatism still dictates splenectomy in cases in which there is any doubt about appropriate management.

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EDITORIALS

Scientific Methods in Medicine

THE SCIENTIFIC METHOD is often spoken of as though it were something immutable, objective and uniquely revealing about nature and humankind. In medicine we think of the scientific method as being productive of dependable knowledge about how to prevent or repair human ills. We tend to look somewhat askance at diagnosis and treatment which is not scientific, that is not established as valid by the method of science. No doubt this is because modern science has brought medicine into a new era of enormously greater understanding and achievement.

If one takes even a cursory look at the history of science one is hard put to find any simple definition of just what is science or what is scientific method. Rather one gets a sense that scientific methods change with or are adapted to the problems to be solved. A basic criterion seems to be whether or not a method works at a particular time for a particular problem. In this sense it is probable that throughout its history medicine has generally reflected the science of its times. Certainly physicians have always tried to separate what works in diagnosis and treatment from what does not, and to this extent medicine has always been scientific.

But modern medicine considers itself more scientific than the medicine that preceded it, and no doubt this is so. It has accepted in principle the purist approach of what might be called linear science, where a cause must be shown to produce a predictable effect in a given or controlled set of circumstances. This is the method that underlies such things as Koch's postulates and the more modern prospective double-blind studies or experiments. This method has made possible many of the major scientific advances in modern medicine. But it has drawbacks. It is difficult, often impossible, to control all of the variables in a given study or experiment, and the linear process often takes time—and too often too much time. Results are needed sooner, not later, to be useful in medical practice.

A second method is coming into increasingly wide use. It draws conclusions that seem to work from epidemiologic data. An example of this is the association which has been shown statistically to exist between cigarette smoking and lung cancer. The method circumvents the need to prove in linear fashion that some substance in cigarette smoke is the cause of lung cancer. Indeed the method seems more horizontal than vertical or linear, in that it infers rather than proves cause and effect by documenting statistical coincidence. But it meets our criterion for a scientific method because it works. It has been shown that when certain groups increase their smoking the incidence of cancer goes up and when others reduce their smoking the incidence goes down. And it significantly foreshortens the time and cost that would be necessary to establish this relationship by a more traditional statistically significant prospective study.

It is suggested that in medicine we may be on the verge of needing yet another scientific method that works. In most situations in health and illness many changing factors are at work at any given moment and they are in dynamic interaction with one another. Here the causes and effects are multifactorial. At hand is a rapidly developing electronic technology which is capable of making almost instantaneous calculations involving many

moving or changing elements. It is possible, and to be hoped, that this technology or something like it will make possible yet another scientific method for medicine which can be applied to the study of the ever-changing, interacting and as yet poorly understood multifactorial aspects of health and disease. Such a method is sorely needed.

It seems obvious that there is more than one acceptable scientific method in medicine and that more are probably needed. It is suggested that a basic criterion of whether a method is scientific or not is whether it works for the purpose intended. For medicine it is essential that methods be developed that work well enough, even if not perfectly, and that they produce timely results in terms of the life span of both physicians and their patients.

—MSMW

Scurvy, Ascorbic Acid and Megavitamins

DESPITE ADVANCES in medicine, improved living conditions and nutrition, scurvy still exists in urban centers.[1] A great deal is now known about its pathophysiology. Severe ascorbic acid deficiency affects the metabolism of collagen, folate and iron. The most important defect in scurvy is abnormal collagen biosynthesis. It leads to the escape of blood into tissues, the key clinical feature.

In this issue Richard Vilter, distinguished professor of medicine of the University of Cincinnati, reports on the history and clinical aspects of scurvy. Long familiar with the condition, he gives a detailed, scholarly account of the biochemistry of ascorbic acid deficiency. He lists the diseases, from common cold to cancer, for which ascorbic acid, usually in very large doses, has been tried and reports how these various applications are long on theory and short on solid data. He also points out that megadoses of ascorbic acid may not be innocuous. The only reasonable indication for the prescription of a large dose of vitamin C is the Ehlers-Danlos syndrome, which is caused by a congenital, qualitative defect of collagen. Vilter's article makes it clear that vitamin C, similar to vitamin B_{12}, has an extremely narrow range of effectiveness: In deficiencies, administration of these vitamins produces spectacular clinical successes, but these triumphs are not transferrable to conditions where no lack exists. It may be tempting to use potent agents that are relatively free from side effects in large doses where cures as yet do not exist, but this romantic approach to clinical problems does not work.

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Shortcuts to Athletic Success?

FROM THE ARTICLE "Chemical Warfare: Drugs in Sports," elsewhere in this issue, it would appear that scientific documentation of efficacy is not among the criteria used in selecting chemical or nutritional ergogenic aids for athletes. While some of the substances have legitimate uses for persons who are less than healthy (for example, packed red cells for anemic patients and anabolic steroids for those who are cachectic), it seems a perversion of science to administer them to the fit in hopes of attaining suprafitness. In spite of documented undesirable side effects and (generally) undocumented desirable results, the search for new substances and the continued use of *traditional* chemical aids apparently go on unchecked—save for the efforts of the Olympic drug testing group.

The multimillion dollar testing for the presence of "doping substances" apparently has had some deterrent effect; there have been fewer medals withdrawn in recent years. Yet if this deterrent effect truly exists—and is not just temporary avoidance of prohibited substances during selected international events—why then do the testing procedures become more comprehensive, sophisticated and expensive each year?

Elaborate drug testing may indeed aid in ferreting out cheaters but it also piques the curiosity of that group of zealous competitors who would dearly love to find a shortcut to athletic excellence. It is difficult to convince these people that the testing is done to avoid serious health hazards rather than to discover the presence of substances that might indeed enhance performance. In short, publicizing the use of elaborate testing methods might actually encourage the use of the substances for which the tests are being done.

Although dealing with the effects of *doping* in internationally competitive athletes is not among

the issues associated with the day-to-day practice of medicine, managing patients seeking shortcuts to fitness is an increasing problem. Ergogenic aids of a more subtle variety are not uncommonly used by average participants in sports or recreational activities. Examples include the use of diuretics to aid high school wrestlers in "making weight," antihistamines to enhance *bulking-up* and tranquilizers to control the (normal) anxieties associated with athletic competition. One might also include the indiscriminate use of anti-inflammatory preparations or cortisone injections for overuse tendinitis, when a day or two of rest or a proper rehabilitation program might better treat that problem. Notably, these substances are not mysterious compounds obtained through an athletic *underground,* but rather prescription medications administered by physicians usually as a sincere effort to help a patient achieve athletic goals. Yet in these and similar instances the indications for the use of these drugs are hardly less questionable than the indications for massive doses of vitamin E, liquid protein, nutrient preparations or vitamins containing strychnine.

Responsible, successful coaches and athletes are the first to note that athletic achievement is primarily the result of arduous, long-term training and conditioning. Unfortunately, the increasingly large population of recreational athletes have not gotten this message. A tennis player, for example, might well prefer to believe that the treatment of choice for his or her tennis elbow is repeated cortisone injections, rather than spending four hours on the court learning to hit a backhand shot properly.

As the fitness craze grows and the number of recreational athletes seeking medical care increases, the opportunities to use or misuse ergogenic aids will also increase. Physicians will be faced with more questions regarding training and conditioning methods, injury prevention and other sports-related medical factors. Consequently, physicians must be prepared to respond to these questions because herein lies a key to the long-term management of many sports-related problems.

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CASE REPORTS

Refer to: Moss RA, Mena RR, Morin RJ: Atherosclerosis and a coronary artery bypass operation in a woman with von Willebrand disease. West J Med 133:515-517, Dec 1980

Atherosclerosis and a Coronary Artery Bypass Operation in a Woman With von Willebrand Disease

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VON WILLEBRAND DISEASE* (VWD) is a common familial bleeding disorder characterized by low levels of factor VIII and decreased adhesion of platelets to vascular subendothelium. The platelet defect is a result of low levels of factor VIII—von Willebrand factor (VWF) that are required for normal adhesion. Both clinical and laboratory findings can be variable even within families, but in general there is spontaneous and trauma-induced purpuric-type bleeding and excessive loss of blood during surgical procedures. Bleeding is generally treated with cryoprecipitate or plasma, but because of patient variability no specific therapeutic guidelines are available that cover all situations. Of particular concern are the requirements of a given patient during and after major surgical procedures.

The case of the patient discussed below illustrates two points: Although the patient has documented VWD, she was able to undergo, with cryoprecipitate coverage, a coronary artery bypass operation without complications. Furthermore, in view of recent work suggesting an important role for platelets in the development of atherosclerosis, the severe coronary artery disease seen in our patient raises questions about a protective effect of VWD in humans.

*THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

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ABBREVIATIONS USED IN TEXT

factor VIII_{AHF} = factor VIII coagulation activity
factor VIII_{Ag} = factor VIII antigen
VWD = von Willebrand disease
VWF = von Willebrand factor

Report of a Case

A 63-year-old woman was admitted to hospital in February 1979 for elective cardiac catheterization. She had had a three-year history of angina pectoris which had been treated with nitrates, but she had experienced a recent increase in the frequency of her pain. Risk factors included only adult-onset diabetes mellitus and mild hypertension of long duration. Medications being taken by the patient included chlorpropamide, propranolol and nitroglycerine.

Cardiac catheterization showed severe triple-vessel coronary artery disease with excellent left ventricular function. The day following the procedure she was found to have a large hematoma at the catheterization site in the right groin, associated with a drop in hematocrit from 40 percent to 31 percent. Careful questioning at that time disclosed a long history of mild bleeding, including easy bruising, menorrhagia and excessive bleeding after a hysterectomy and a tonsillectomy. Her sister and daughter both had similar bleeding problems. The following tests were carried out at once: prothrombin time (PT), activated partial thromboplastin time (PTT), thrombin time and platelet count. Results were within normal limits. The bleeding time (Simplate; General Diagnostics, Morris Plains, NJ) was 7 minutes. Two units of fresh frozen plasma were administered and the bleeding stopped. A laboratory evaluation two weeks later gave the following results: factor VIII coagulant activity (factor VIII_{AHF}) 45 percent, factor VIII antigen (factor VIII_{Ag}) 15 percent and glass bead retention 14 percent (normal,

greater than 25 percent). Chlorpropamide and propranolol therapy was discontinued. A repeat bleeding time was 5 minutes. Platelet aggregation in response to adenosine diphosphate (ADP), epinephrine, collagen and 1.2 mg per ml of ristocetin was normal. The administration of 500 ml of cryoprecipitate (approximately two units of factor VIII per ml) resulted in factor VIII_{AHF} levels of 80 percent after one hour and 100 percent at 16 hours postinfusion, but without improvement in glass bead retention. The patient's sister and daughter were examined, and both had bleeding times of approximately 20 minutes, decreased ristocetin aggregation and factor VIII_{Ag} levels of 13 percent and 15 percent, respectively.

In April 1979 the patient underwent a triple-vessel coronary artery bypass operation. Extracorporeal circulation lasted 152 minutes with heparin anticoagulation. She received 1,000 ml of cryoprecipitate two hours before the operation and 100 ml intraoperatively. Care was taken to obtain adequate local hemostasis during the procedure. Thereafter she received 500 ml every 12 hours for five days, at which time the cryoprecipitate was discontinued. No excessive bleeding occurred during or after the bypass operation. She is undergoing cardiac rehabilitation and was free of pain on follow-up.

Comment

The diagnosis of VWD was established on the basis of low values of factor VIII_{AHF}, factor VIII_{Ag} and decreased glass bead retention as well as a delayed rise in factor VIII_{AHF} after transfusion with cryoprecipitate. Unusual features were the normal bleeding time, PTT and platelet aggregation with ristocetin. However, it is clear that in many patients with this disorder abnormalities of these screening tests are not observed,[1] yet as seen here, a significant bleeding diathesis may still exist.

Although successful aortic valve replacement has been described in patients with hemophilia[2] and VWD,[3] this is the first published report of a coronary artery bypass operation in a patient with VWD. The case illustrates the ability to carry out such procedures safely without excessive loss of blood. Although the bleeding in VWD generally responds well to cryoprecipitate, there are no specific guidelines for the amount needed. Because a cardiac operation was intended and the patient had a history of abnormal bleeding, we elected to use large doses of cryoprecipitate before, during and after the procedure. In the past, we have successfully used smaller amounts of cryoprecipitate (100 to 200 ml) for less complicated surgical procedures and it is possible that less replacement therapy would have been effective in this case. It is clear, however, that patients with VWD can undergo major surgical procedures even with anticoagulation if coverage is adequate and good local hemostasis is achieved.

Several lines of evidence suggest that platelets play a role in the development of atheroselerosis. Ross and co-workers[4] have shown that a platelet factor stimulates the proliferation of smooth muscle cells in tissue culture, and pigs with VWD exhibit fewer atheromas than controls.[5] In addition, thrombocytopenia as well as an antiplatelet agent, dipyridamole, have been shown to inhibit formation of lesions in experimental models of arteriosclerosis.[6,7] A corollary to these findings is the presumption that defects in platelet function may protect humans from atheroselerosis. However, Silwer and colleagues[8] described severe atheroselerosis in their findings at autopsy of two of three patients who had VWD, and probable atheroselerosis based on clinical findings in several others. Obviously, the severity of VWD may be important in determining the degree of protection. Our patient had consistently normal bleeding times and it is likely that she is heterozygous for VWD. This may be especially relevant in view of a recent report[9] which suggests that resistance to cholesterol diet-induced atheroselerosis is present in homozygous (factor VIII_{Ag} undetectable) but not heterozygous (factor VIII_{Ag} approximately 40 percent) VWD pigs. Thus, it appears that only extremely low levels of factor VIII_{Ag} may be protective. Because our patient had only mild VWD as well as significant risk factors for the development of atheroselerosis, it is not possible to assess any protective effect of VWD in this case. However, it is clear that severe atheroselerosis can develop in persons with VWD and that coronary artery bypass operations can be safely carried out in these patients.

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Refer to: Wilson DR, Cotie RW, Bailey LL: Boerhaave syndrome: Lifters' liability. West J Med 133:517-519, Dec 1980

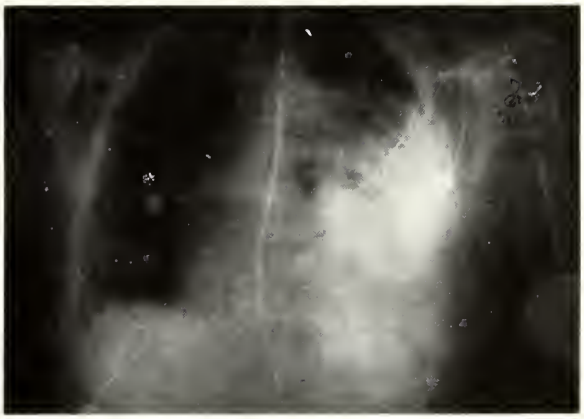

Figure 1.—A roentgenogram of the chest taken at patient's admission to Loma Linda Hospital, showing evidence of contrast medium in the left pleural space.

Boerhaave Syndrome: Lifters' Liability

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In 1723 Dr. Hermann Boerhaave was summoned to the bedside of the Grand Admiral of Holland, Baron Van Wassenauer.[1] The gluttonous baron had suffered severe epigastric pain during self-induced vomiting. Boerhaave found the patient in great pain, but with little other than tachycardia found on examination. The doctor gave a hopeful prognosis. The Admiral, however, expressed the opinion that something had burst inside and he would surely die, which he did 18 hours later. An autopsy showed complete esophageal disruption with fluid smelling of roast duck in the pleural cavities.

Recently, we treated a man with rupture of the esophagus that resulted from an unusual cause. We report the case below.

Report of a Case

In 1978 a 73-year-old clergyman experienced sudden, severe retrosternal pain radiating to the back while lifting the spare wheel and tire into his automobile. He promptly went to his local hospital and was found to be hypotensive (40 mm of mercury, systolic) and mildly febrile (38.1°C; 100.6°F). His lungs were clear, but bilateral splinting was noted, and there was generalized abdominal tenderness with absent bowel sounds. Diagnostic possibilities on admission included myocardial infarction and an acute condition within the abdomen. Findings on an electrocardiogram were normal, and x-ray studies of the chest and abdomen showed no abnormalities. Suspicion of upper gastrointestinal leakage prompted a radiographic study which showed extravasation of the contrast medium (Gastrografin, a diatrizoate meglumine and diatrizoate sodium preparation) into the mediastinum and established the diagnosis of esophageal rupture.

On physical examination after transfer to Loma Linda University Medical Center, the patient was pale, anxious and obviously in severe pain. His respirations were shallow and he insisted on maintaining a sitting position, avoiding any movement. Minimal subcutaneous emphysema was present in the left supraclavicular fossa. Breath sounds were decreased over the left side of the chest. On admission an x-ray study of the chest (Figure 1) showed contrast medium in the left pleural space, indicating erosion of mediastinal pleura since the previous film. Further intravenous fluid replacement stabilized his hemodynamics, and an operation was done ten hours after the onset of pain. His chest was opened through the sixth left intercostal space. Approximately 1,500 ml of brown fluid containing food particles was aspirated. The

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left-sided lower esophageal tear (Figure 2) was closed in layers with polyglycolic acid sutures. There was no hiatus hernia or esophageal pathological condition other than the laceration. After copious saline irrigation and insertion of chest tubes, the thoracotomy was closed. Parenteral hyperalimentation was initiated. A radiographic study after oral administration of Gastrografin on the fifth postoperative day (Figure 3) showed no leak, and the patient was given fluids orally soon after. An excellent recovery ensued, marred only by progressive azotemia that cleared after transurethral resection of his grossly hypertrophied prostate.

Figure 2.—A view of the ruptured esophagus with pouting mucosal edges and mediastinal soiling.

Figure 3.—A roentgenogram of the repaired esophagus five days after the operation, showing no evidence of leakage.

Comment

Esophageal rupture unassociated with external trauma, operation, instrumentation, foreign body or overt esophageal disease has been inappropriately described as "spontaneous perforation of the esophagus."[2] The eponym Boerhaave syndrome* is less cumbersome, is widely accepted and does not specify cause.

Most cases (more than 95 percent) are caused by vomiting and the causative term emetogenic may be appropriately applied. Excessive food and alcohol ingestion is usual in such cases of esophageal rupture. Nonemetogenic Boerhaave syndrome, occurring in less than 5 percent of cases, has been described in association with asthma, epilepsy, compressed-air accidents, forceful swallowing, abdominal blows, and straining during parturition or defecation. Lifting is conspicuously absent from many reports[3-7] that list various other causes and probably accounts for less than 1 percent of cases of Boerhaave syndrome. All cases of this syndrome have in common increased intraluminal pressure, which may be either primary (such as compressed-air accidents or forceful swallowing), or secondary (such as increased intra-abdominal and intragastric pressure transmitted across the gastroesophageal junction). Risk of rupture is increased if esophagogastric competence is compromised while the upper esophagus is closed by contraction of wall muscle or the inferior pharyngeal constrictor. The mechanism is described by the terms pressure, pneumatic and barogenic rupture. Experiments by Mackler[8] and others with pneumatic distention of the cadaver esophagus have shown a predilection for distal (lower) left-sided rupture. This was true both in situ and after removal of the organ. Weakness is evidently related to the distribution of esophageal muscle.

Previous reports of Boerhaave syndrome produced by lifting are of interest. Rolleston[9] noted the case of "a coachman, aged 50, of temperate habits [who] was in good health until 1 PM on August 1, 1891, when in making a strong muscu-

*THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

lar effort in lifting a carriage experienced great pain in the abdomen." Death ensued the following day and autopsy results showed typical findings. Griffith[10] reported a similar case in a 46-year-old man who experienced sudden severe pain while lifting a 50-pound bundle. The man died nine hours later and autopsy findings confirmed rupture of the lower left side of the esophagus. Patton and co-workers[11] described a case of assumed Boerhaave syndrome after lifting. However, the patient died before operation and the diagnosis was not confirmed.

Treatment consists of early operation with closure of the esophageal rupture, generous lavage and drainage of the pleural space. Hyperalimentation may be a useful adjunct. Chest-tube drainage and hyperalimentation without thoracotomy may be indicated in advanced or neglected cases.[12,13]

Although liability to barogenic rupture of the esophagus during lifting is limited, if incurred the liability is grave. Prospects of survival deteriorate steadily with each hour that the person remains untreated. Early diagnosis and treatment are the keys to successful management. It is therefore emphasized that Boerhaave syndrome must be considered in the differential diagnosis of any patient experiencing sudden severe abdominal or chest pain while lifting or straining.

Summary

Esophageal rupture associated with lifting is uncommon. Reported herein is such a case managed surgically with a successful outcome. Sudden severe chest or abdominal pain associated with lifting suggests the possibility of esophageal rupture. This is believed to be the first recorded instance of survival of a patient with Boerhaave syndrome that was produced by lifting.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

From IM Morphine to PO Methadone

To the Editor: A 37-year-old man with a 17-year history of intravenous use of heroin was admitted to our surgery service with a massively swollen and painful hand and arm. The arm also had many deep draining stasis ulcers. Geelhoed[1] and Neviaser[2] have described this "puffy hand and arm" condition as a consequence of chronically impeded lymphatic and superficial venous drainage secondary to the scarring produced by the inflammatory effects of the adulterants commonly used as fillers in illegal drugs.

Initially morphine, not methadone, was used to control the pain and prevent withdrawal symptoms because our pharmacy was not licensed to issue methadone for maintenance purposes. In addition, a one-day trial of methadone, 60 mg given orally, from the local methadone clinic resulted in withdrawal symptoms and inadequate pain relief. (Our local methadone clinic would not dispense more than 60 mg of methadone for oral administration per day per patient.)

We found that morphine, 15 mg given intramuscularly every six hours, prevented withdrawal symptoms, gave no euphoria and provided adequate analgesia, especially during dressing changes. Detoxification began on the fifth hospital day when the edema had been moderately reduced and the arm was less painful. The treatment plan had three parts: (1) detoxify with morphine to a dose equal in analgesia and control of withdrawal symptoms to 60 mg of methadone given orally, (2) enter the patient in the local methadone detoxification clinic's program (and by special arrangement permit them to administer the methadone in our hospital) and (3) pursue the inpatient care of the arm.

The dosage relationship between orally given methadone and parentally administered morphine was not known. However, because methadone for oral administration is about half as potent as morphine for intramuscular administration, and because morphine and methadone given intramuscularly are roughly equally potent,[3] it seemed reasonable that a methadone (orally) to morphine (intramuscularly) ratio should be 2:1. Therefore 60 mg of morphine intramuscularly was equal to 120 mg of methadone by mouth. Looking back, the failure of the one-day methadone trial was understandable.

The intramuscularly given morphine dose was then reduced by an average of 2 mg each day to a final dose of 28 mg per day. The change to 55 mg of methadone given orally every morning was made and no signs of pain or withdrawal symptoms were noted. The methadone dose was to have been reduced 5 mg per day, but unfortunately, on the second day of methadone use, a severe allergic reaction (generalized edema and oliguria) developed.[4,5] Methadone administration was stopped and all the symptoms resolved within 24 hours. Meanwhile, an equivalent morphine dose was calculated and the switchback made.

No further medical problems arose, but regrettably the patient's hospital stay spanned the first of July, when new residents and students entered the service and the older ones—myself included—were transferred to other services. The disruption of relationships and discontinuity of care that these changes can produce were overwhelming to this patient, who, five days later, left the hospital—two days before the detoxification would have been completed.

Though the psychological management of this case was unfortunate and tragic, the methadone-to-morphine formula was successful. As for the arm, the swelling was much less and the ulcers were all healing nicely.

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Methicillin Rash in Infectious Mononucleosis

To the Editor: An interesting phenomenon occurring in patients with infectious mononucleosis is the increased incidence of the rash associated with ampicillin and its derivatives.[1-4] This rash does not occur with other penicillin derivatives. I would like to report a case of the ampicillin rash in a patient with infectious mononucleosis with the subsequent development of an identical rash to methicillin.

Report of a Case

A 32-year-old white man was seen in the hospital's outpatient department with exudative pharyngitis associated with lymphadenopathy. Findings on initial evaluation were compatible with streptococcal pharyngitis and therapy was started with 250 mg of ampicillin given four times a day. There was no prior history of penicillin allergy. The patient came to the emergency room three days later with exudative pharyngitis of a more severe degree and a diffuse morbilliform rash over his extremities and face. Laboratory examination showed a leukocytosis of 15,726 per cu mm with a lymphocytosis and more than half of the leukocytes atypical. Monospot test was strongly positive. A diagnosis of infectious mononucleosis was made and administration of ampicillin was discontinued. The rash disappeared during his ensuing hospital stay. While he was in hospital, corticosteroids were required for obstructive symptoms referable to extreme pharyngitis and he was discharged on a regimen of 20 mg per day of prednisone. Three days later, the patient received a minor cut on his right hand; redness and swelling developed. On examination, the patient was considered to have cellulitis of the right hand. He was admitted and therapy was started with 6 grams per day of methicillin. Within a day a rash developed identical to that seen previously after ampicillin had been administered. Laboratory results were still compatible with ongoing infectious mononucleosis. The medicine was discontinued and the rash promptly disappeared. The patient made an uneventful recovery.

Comment

The only aspect of this case remaining to be resolved was whether the patient was allergic to methicillin. Three months later, a rechallenge of the patient was conducted. All possible complications that might occur, including anaphylaxis, were clearly explained to the patient. He was readmitted to the hospital at which time results of a complete blood count and monospot test were no longer consistent with ongoing infectious mononucleosis. He was challenged with a 2-gram dose of methicillin given intravenously; this was repeated six hours later. No rash, pruritis or other sign consistent with allergy to methicillin developed.

This case is illustrative of the textbook teaching of the increased occurrence of ampicillin rash and infectious mononucleosis. However, a search of the literature fails to produce any evidence of a similar phenomenon with synthetic penicillinase-resistant penicillin derivatives. I submit that clinicians should watch for this combination of occurrences taking place in patients with infectious mononucleosis in whom treatment with semisynthetic penicillins is required.

In conclusion, clinicians should be wary of the use of ampicillin in undiagnosed cases of exudative pharyngitis. In addition, one should also be aware of a similar reaction with methicillin and possibly other semisynthetic penicillins. The reaction occurs in patients with no known allergy to penicillin who have successfully received penicillins in the past. A large center review of charts of patients with infectious mononucleosis who have received semisynthetic penicillins is in order to confirm the observations found in this single case.

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Evaluating Executive Health Examinations

To the Editor: I read with interest Dr. Richard Babb's article in the September issue ("An Evaluation of the Executive Health Examination"), and I believe it warrants comment. I have some serious reservations about the conclusion that "such examinations are worthwhile."

In constructing his study, Dr. Babb chose to

"avoid interobserver variability" by reviewing all of his own charts himself. As he has stated, this will certainly decrease such variability, but I am concerned that other unconscious biases may be introduced any time an investigator assesses the value of his own work by reviewing that work himself.

A second possible problem may occur in that one patient may have several diagnoses. Thus, when Dr. Babb states that 8 percent of the patients seen were obese and 6 percent had hypertension, if a patient had both obesity and hypertension (potentially a common occurrence) the numerator of the statistic "percent of patients" (which really seems to be the number of diagnoses made) would be spuriously elevated faster than the denominator of that same fraction (which is the total number of patients).

Third, in examining the diagnoses made in the 420 executives, one might observe that (as the author does state) many of the diagnoses were already known to the patients or to their physicians. Thus, a statement that 30 percent of the executives were found to have at least one disease does not necessarily support the conclusion that executive health examinations are worthwhile, since a much smaller percent (see below) of these diagnoses were new and actually discovered by means of the executive examination.

One could also observe that many of the diagnoses that were new could have been made without the extensive and expensive executive health program. The 5 new obese, 20 new hypertensive and 6 new glaucoma patients, for example, could easily have been detected without such a costly program by a good nurse. To state prevalence rates of such diseases as justification for executive examinations ignores the fact that these diseases could be detected in much more cost-efficient ways.

In reexamining Dr. Babb's data, it may be seen that there were indeed 46 new diagnoses made which could conceivably have been made best by a physician doing a good examination, and could thus potentially help validate the executive health examination. (These new diagnoses were 3 new cases of depression, 6 of alcoholism, 4 of anxiety, 8 of arthridities, 8 of hernia and 17 of miscellaneous disorders.) If one assumes the worst, that there were 46 different people who had these 46 diagnoses, then approximately 10 percent of the population screened would have been found to have a new diagnosis. One might argue that a 10 percent rate of new diagnoses indeed justifies the costly program, but it does seem less impressive than the 30 percent that Dr. Babb had quoted.

If the corporations and executives involved were accurately informed that (1) (as Dr. Babb admits) the pulmonary function studies, x-ray films and electrocardiograms were "of little benefit," that (2) the connection between any laboratory abnormalities and improvement of health is unclear and that (3) many of the diagnoses could be made by much simpler and less expensive screening tests, perhaps the corporations and executives would request such programs less often.

Possibly part of the large sum of money spent (400 times $300 equals $120,000 a year) could better be targeted on specific, much simpler health screening procedures, and the remainder on health educational programs which might be of more benefit to patients.

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* * *

To the Editor: I take issue with Dr. Richard R. Babb's article "An Evaluation of the Executive Health Examination," because it ignores cost-effectiveness.

It should be emphasized that the costs of the program were $250 to $350 per examination. The major findings were obesity, hypertension, depression, alcoholism and anxiety, as well as such poor health habits as sedentary life-style and smoking. The most poignant remark in the article, in my opinion, was "When an attempt was made by me to decrease the number of screening tests, executives were often upset, and their companies asked that the program not be changed."

There is a major effort on the part of medicine to clean its house. In the context of a society applying increased pressure on the "health care delivery" system to contain costs, this article is not helpful. It is redeeming, however, if we realize that the pressure in this unique situation was to spend as much money and time as possible. By so doing the major findings, as I have interpreted them, are remarkable indeed. They are the ones that would take a paramedic with some background in psychology about 30 minutes to make at a cost of perhaps $20.

The concept of an executive health examination in this day and age is archaic and carries the

stigma of elitism. The average health consumer must find this offensive. We need all the allies we can get—especially the average man.

BARRY D. ORVELL, MD
Oakland, California

* * *

To the Editor: In regard to Dr. Richard Babb's article, "An Evaluation of the Executive Health Examination," I have the following comments:

Surely any competent physician does not need to spend $250 to $350 in order to diagnose obesity, emotional illness and drug dependence. On reviewing Dr. Babb's data, I see virtually no *significant* illness that could not have been discovered by a simple history and physical examination with perhaps the addition of tonometry.

I am sure, as Dr. Babb states, that corporations are satisfied with this program. It is relatively easy to spend money for high-technology screening tests in the mistaken belief that testing is equated with health.

Executives, like any other workers, are subject to occupational hazards. Certainly, if a worker is being exposed to lead, for example, some attempt would be made to reduce exposure. In the same way, why not take the money saved by streamlining these costly executive health examinations and attempt environmental modification to reduce exposure to executive occupational hazards: two-martini lunches, smoking, emotional stress and lack of exercise.

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* * *

To the Editor: After analysis of his data, Dr. Richard R. Babb concludes that the executive health examinations discussed in his article are indeed worthwhile. In this era of cost-effective medicine and appropriate utilization of medical resources, I am in absolute disagreement with this conclusion.

One must first understand that the patient population concerned has excellent access to the health care system if and when significant symptoms arise. A diagnosis such as arthritis in 3 percent of patients, found by "physical findings [in the hands] and x-ray studies of the spine, hip, and knees" is not a very good *pickup* by a screening study because the treatment is essentially symptomatic (one cannot change the course of degenerative joint disease) and, in this patient population, those patients who are symptomatic will go see their doctors.

Similarly, if one looks at the combination of obesity, depression, alcoholism and anxiety (should one include smoking?), are these really new findings in a health screening examination? Dr. Babb himself had seen 218 of the 420 patients in previous years. One would think that these problems could have been picked up earlier by himself or his colleagues who saw the other 202 patients. Do these findings really belong in his statistics of diseases detected by the particular health examination he is studying? Yet, they account for 18 percent of his calculated 30 percent. Indeed, for these illnesses, the treatment is (frustratingly) so poor that the value of finding them is, in itself, somewhat questionable. Significant findings (a term which I will define as those that can be used in some way that will have a likelihood of benefitting a patient's health), including hypertension, glaucoma and inguinal hernia, occurred in only 9.5 percent of patients.

The cost of these 420 examinations was $126,000. For $126,000, one could have a technician march through every corporate office in Palo Alto measuring the blood pressure and intraocular pressure of every executive, secretary, elevator operator and cleaning person (possibly even commenting along the way "You're too fat—lose weight" or "Stop smoking") and pick up almost all of the significant findings of Dr. Babb's group, as well as serving a larger group of people who generally have less access to our health care system (and more need for free examinations) than do a group of corporate executives.

LONNY SHAVELSON, MD
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* * *

Dr. Babb Replies

To the Editor: As mentioned in the opening remarks of my paper, there is considerable debate revolving around the concept of annual, or even periodic, health examinations. Critics, however, often equate an executive health examination with the checkup of a private patient, and this is not appropriate.

Corporate leaders understand "cost-effectiveness" far better than most doctors and, thus far, have felt their money well spent promoting the health of employees. Considerable time and money is spent on executive training and future management strategy. Considerations of executives' emotional and physical health are important in

this planning, above and beyond any benefit to the individual persons involved.

In contrast to several other clinics, we have never advertised our Executive Health Program in the public media or in professional journals. Nonetheless, our program has grown steadily over the years and continues to do so.

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Medical Judgments and Telephone Operators

To the Editor: Recently I spoke with some employees of a telephone answering company that serves physicians. I was amazed at the medical judgments physicians expected them to make. For example, a pregnant woman reported to one answering service operator that her bag of water had broken, but she did not have any labor pains. She wanted to know if she should go to the hospital. The telephone operator told me that she did not have specific instructions for such cases, but that it was typical of the kind of decision she was expected to make for doctors.

I believe such decisions should be made by one of the doctors' aides if the doctor is unable to take such calls. We must remember several facts about answering service personnel: (1) Experienced telephone operators with a college education are much scarcer than experienced doctors' aides with similar higher education. (2) Few, if any, operators have had any special training in medical offices. (3) Graveyard shift personnel are very hard to find.

I urge doctors who may receive after-hours calls requiring medical judgment to insist these calls be referred to themselves or to their own personnel.

ARTHUR F. GREENWALD, MD
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Thoughts on Mandatory CME

To the Editor: This letter is prompted by my just completing this morning the tedious task of filling out the continuing medical education (CME) forms for the year of 1979-80, kindly supplied by the California Medical Association, so that I might continue to practice medicine in California and allegedly to prove that, after all, I am a competent physician, let alone a specialist in orthopedic surgery with a subspecialty in pediatric orthopedics. I note that one gets brownie points for publications and for research, as well as for teaching. No one knows, however, whether the research is really worth any points, nor does anyone on the state's Board of Medical Quality Assurance really know whether the publications are worthwhile or significant. Further, no one knows whether I listened to all of the lectures that I went to, and what is worse, who knows how much has been retained?

I believe that CME is a childish and anti-intellectual enterprise, not befitting professionals who are supposed to be mature. Behavioral scientists tell us that expected behavior is the potent force. If I look at CME and the expected behavior, I would anticipate that physicians would either become more childlike, deceitful or cynical, or all three together.

One reason that I am prompted to write this letter now is that last night at home I was preparing a lecture on contemporary problems in congenital dislocation of the hip for my colleagues in the Santa Clara Orthopaedic Society at their monthly meeting tonight. It is humbling to point out that all of the major contributions in increasing our knowledge of congenital dislocation of the hip, its prevention and its treatment, have come in the past quarter of a century from foreign physicians—Ortalani (Italy), von Rosen (Sweden), Barlow (United Kingdom), Pavlik (Czechoslovakia) Salter (Canada), Klisic (Yugoslavia) and Chiari (Austria). What is depressing about the United States' endeavor and its ability to overorganize anything is that we are drying up creativity, which is derived from thought and reflection. We have become players according to the rules. I hate to think where the computer industry in this country would be if they had computer science education forced down their throats.

The second reason for writing about this subject is that we have no objective evidence whatsoever that the increase in malpractice claims or awards has slowed any as a result of CME by fiat. If there has been a reduction, I am unaware of it and have not seen data about it.

The third reason for this letter is that some of our younger faculty have asked repeatedly why the senior faculty do not rear up and tell the truth, or at least raise a question about what seems to be childish and time-consuming forced CME—a classic example of substituting form for substance, and incurring increased costs as well. I guess after 25 years of practice in California, I would qualify as a "senior."

I would hope that this issue could be looked at carefully and objectively by the profession and its leadership. Before CME we had all of the postgraduate educational institutions established: hospital rounds, the clinicopathologic conferences, state medical associations, the American Medical Association and the majority of the national academies, as well as the schools of medicine—which have always been engaged in postgraduate medical education. Why people want to learn and how they learn and how this translates into practical behavior and action is another subject well worth considering.

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EDITOR'S NOTE: *The House of Delegates of the American Medical Association has called for a moratorium on the further extension of mandatory continuing medical education, or any mandatory reexamination or recertification programs, pending evidence of their effectiveness in upgrading physician competence.*

—MSMW

Diagnostic X-ray Studies During Pregnancy

TO THE EDITOR: In their Occupational Medicine Epitome "Low Level Radiation Exposure" in the August 1980 issue (page 150), Drs. Hasso and Moore attempt to allay anxieties about small amounts of diagnostic radiation during pregnancy by stating: "The extra risk from diagnostic radiation [compared with natural radiation] is . . . negligible." They offer as reassurance that if a birth anomaly were observed, it would not be possible to state whether or not it was caused by cosmic or diagnostic radiation. Their assertions seem illogical from either a primary care or public health point of view. A pregnant woman who has a diagnostic x-ray study is interested neither in the cosmic ray induced mutation rate nor in the fact that a future dysmorphologist would be unable to tell her the probable cause of her child's birth anomaly. She is interested in knowing that her risk of a poor pregnancy outcome is one to five in a thousand for each radiograph of her abdomen. It is for her to decide whether or not this risk is "negligible." From a public policy standpoint, if each fetus of the 300,000 term pregnancies in California last year had been exposed to one rad, the statistics that Drs. Hasso and Moore cite would predict 300 to 1,500 fetal abnormalities per year—again not a negligible effect. While this is a "worst-case" scenario, it is a possibility if each clinician ordering an abdominal x-ray film for a pregnant patient were to think of the risks as "negligible."

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* * *

Drs. Hasso and Moore Reply

TO THE EDITOR: We did not intend to imply that diagnostic x-ray studies should not be used prudently, even though the risks involved appear to be small compared with risks we all undertake daily. Nor, did we intend to usurp a patient's right to decide whether or not the risk—a 1 rad fetal dose increasing the chance of a birth anomaly from the natural rate of 4 percent to between 4.1 percent and 4.5 percent—is negligible. Indeed, we subscribe wholeheartedly to the May 1977 guidelines of the American College of Obstetricians and Gynecologists in which it is stated that "the degree of risk involved in an x-ray examination if the person is pregnant, or should become pregnant, should be explained to the patient and documented in her record" (ACOG Statement of Policy as issued by the Executive Board of ACOG, "Guidelines for Diagnostic X-ray Examinations of Fertile Women," approved May 1977, page 3). Of course, if a birth anomaly does arise in such a case it is of no consolation to say that a radiogenic birth defect cannot be distinguished from a nonradiogenic birth defect, as Dr. Jackson points out.

We were merely attempting to educate physicians about the order of magnitude of the risks involved, in an area where we felt there was a scarcity of information needed to place things in perspective. We are completely in favor of having persons informed of the risks of diagnostic x-ray examinations, at both the provider and consumer levels. In this way, instances such as the one in which a physician recommended a therapeutic abortion on the basis of a gallbladder series, where the fetal dose most probably did not exceed 0.2 rad, can be avoided.

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Nevada's Medical School Comes of Age

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THE UNIVERSITY OF NEVADA, RENO (UNR),* Health Sciences Program was authorized in 1969 by an act of the Nevada State Legislature to provide education and training for Nevadans wishing to pursue careers in medicine. The university then developed a school comprising the first two years of medical school. The first chartered class of 32 students entered a two-year basic science program in 1971 located on the UNR campus. Until that time Nevadans who wished to enter the field of medicine had to seek educational opportunities out of state, and relatively few students from the state entered medical school each year.

From 1971 through 1979, nine classes, totaling 392 students, began their medical education at the school. All members of the first five classes at the two-year school transferred to degree-granting programs at 35 medical schools throughout the United States. Many of these students have completed their education and postgraduate training and are now practicing medicine in Nevada and throughout the West.

In December 1976 the Board of Regents of the University of Nevada system unanimously approved "A Proposal for the Development of a Degree-Granting Medical School Initially With Residencies in Primary Care."

The decision to convert to a four-year, degree-granting school was made for several reasons, including (1) increasing difficulties in assuring students' transfer, (2) increasing awareness of the need for community physicians to meet Nevada's health care needs, (3) the national trend, accompanied by financial incentives, for all two-year schools of basic science to convert to four-year, degree-granting schools and (4) the increasing cost to students going out of state to school (estimated at $900,000 annually), as well as increased cost to the state for students who are subsidized out of state, such as those under the Western Interstate Commission on Higher Education program (approximately $720,000 annually).

Following Governor Mike O'Callaghan's strong public endorsement of the conversion of the school, the Nevada State Legislature on April 14, 1977, passed Assembly Concurrent Resolution No. 18 "memorializing the Board of Regents of

Refer to: Anderson FM: Nevada's medical school comes of age (Medical Schools of the West). West J Med 133:526-531, Dec 1980

*University of Nevada, Reno, is a division of the University of Nevada system. Other divisions are the University of Nevada, Las Vegas; Community College division, with four community colleges; and Desert Research Institute, a statewide multifaceted research division.

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the University of Nevada to extend the medical school of the university to a four-year school which would award the degree of Doctor of Medicine." In contrast to the political battles and legislative uncertainties regarding the establishment of the two-year school that occurred in the legislatures of 1967 and 1969, the 1977 Nevada State Legislature enthusiastically endorsed the conversion and further development of the school.

The legislature was undoubtedly influenced in its positive decision by the success of the two-year school, the acceptance of its students into degree-granting institutions and the awareness that both the long-term future success of the school and access to medical education for its young people would be dependent on the state and its university system developing a complete medical education program. The availability of a large conversion grant from the federal government and the support of numerous benefactors probably influenced the legislature's decision as well.

Based largely on the positive action of the Nevada State Legislature, the Liaison Committee on Medical Education voted in 1977 to issue "A Letter of Reasonable Assurance" for conversion. Their decision was based on their review of plans that called for a "Community Based Medical School" utilizing particularly the ample resources of the hospitals in Reno and Las Vegas. The plans outlined to the board of regents, legislature and the liaison committee have been accomplished. The charter junior class students began

Figure 1.—University of Nevada, Reno, School of Medicine's first academic hooding ceremony, May 16, 1980. **(Top)** From left to right: George Smith, MD, founding dean; Reuben Zucker, MD, presenting hood to Karen Arcotta, president of the class of 1980, and Thomas Scully, MD, second dean of the school of medicine. **(Bottom)** Steven Jackson, MD, member of the class of 1980, receiving a copy of the Hippocratic oath from Acting Dean Ernest L. Mazzaferri, MD.

their third-year clinical clerkships in Reno and Las Vegas in the summer of 1978.

In April 1980 the Liaison Committee on Medical Education accredited for two years the newly developed four-year medical education program at the university, thereby granting permission to the Board of Regents of the University of Nevada to grant its first Doctor of Medicine degrees from an accredited school.

This first group of 36 students were awarded the Doctor of Medicine degree on May 17, 1980 (Figure 1). All of these students were successfully matched through the National Residency Matching Program and began graduate residency training throughout the country in July 1980.

The UNR School of Medicine is university and community based. The patients, facilities and staff of its affiliated hospitals and clinics throughout Nevada provide a broad educational base for the school's clinical curriculum. Its affiliation agreements provide access to clinical hospital facilities totaling more than 2,000 beds. In addition to approximately 80 full-time faculty, there are more than 200 community physicians from throughout the state involved in the school's programs, which are designed to provide the students with a broad base in the science and art of medicine.

Students rotate through clinical disciplines in both cities. In addition, all students rotate through a rural elective in their senior year, giving them a broad experience in urban and rural medicine. Small classes, anticipated to include no more than 48 students per year, permit individual attention to students in every phase of their development. These efforts culminated in the graduation of 36 senior students from the school of medicine in May 1980. About two thirds of this class entered primary care residencies in hospitals throughout the country. The others began residency programs representing virtually every major discipline in medicine.

Financing the Conversion

According to Mrs. Edna Brigham, director of development for the medical school, federal conversion funds amounting to $2,400,000 were the major source of support for the conversion to a four-year school. They were supplemented by a W. K. Kellogg five-year grant of $680,304, which made possible the recruitment of qualified faculty and the development of the educational program in the southern part of the state.

The year following approval by the state legislature to convert the school was a complex one with overlapping and interdependent deadlines for accrediting programs and grant applications. The curriculum for the third and fourth years was approved and the clinical Departments of Internal Medicine, Pediatrics, and Family and Community Medicine had their graduate programs approved in time to be awarded residency grants by the Department of Health, Education, and Welfare.

A generous gift of $2,000,000 to the school by a Las Vegas building contractor, Claude I. Howard, provided the impetus to plan a much needed laboratory facility to accommodate the four-year school. This gift was supplemented by a generous grant of $2,000,000 from the Max C. Fleischmann Foundation to complete the capital improvement fund for this building.

In the first year of the conversion (1977-1978) the state appropriated $1,239,000, or 49 percent of the total budget of $2,520,000. In the second year (1978-1979) of that legislative biennium the state appropriated $1,597,000, or 47 percent of the total budget of $3,555,000. In the next legislative biennium the legislature increased its appropriation to $2,867,000 for 1979-1980, and for the year 1980-1981 its appropriation was over $4,095,000, representing 75.2 percent of the total budget. The state of Nevada seems now to have accepted its medical school and its responsibility to provide adequately for medical education needs in the state.

Residency Programs

Simultaneous with the development of the third-year clerkships and fourth-year electives, three primary care residency programs in internal medicine, pediatrics, and family and community medicine were also instituted on July 1, 1979.

Internal Medicine

In July 1979 residency programs in internal medicine were begun in Reno and Las Vegas, with Dr. Ernest Mazzaferri as chairman and Dr. Alfred Thompson, Jr., as director. Six first-year residents began training in each location. Three of the six first-year residents in Reno were UNR graduates. All 12 residents were graduates of medical schools in the United States.

In July 1980 there were 26 residents in internal medicine—13 in Reno and 13 in Las Vegas.

Seven of these 26 are UNR graduates. The program in Reno involves two primary teaching hospitals, Washoe Medical Center and the Veterans Administration Medical Center, plus an ambulatory care teaching center. The three-year residency program in Reno has residents numbering seven, five and one in the respective years of training. The program in Las Vegas is administered at Southern Nevada Memorial Hospital where there are seven, four and two residents in medicine in each respective year of training.

During the past year faculty from Las Vegas and Reno interchanged frequently, making rounds and giving conferences. It is anticipated that there will be an exchange of second- and third-year residents between the hospitals in Reno and Las Vegas. Third-year residents will also spend considerable time in smaller communities, such as Carson City and Elko, and at the Schurz Indian Public Health Hospital.

Participation by practicing clinicians had added immeasurably to the strength of the residency programs, as it had already done in the student teaching programs. The spectrum of pathology and clinical experience has been more than adequate at all participating hospitals and clinics.

Internal medicine residency positions were filled for 1980 and already the school has received more than 50 requests from students around the country for application for the 1981 program.

Family and Community Medicine and Family Practice

The Department of Family and Community Medicine under its chairman, Robert Martin, MD, was founded in 1978, at the same time as other clinical departments, and became involved in training third- and fourth-year medical students. In addition to medical school instruction, the department is also responsible for the operation of a community health center for low-income patients, which is funded by an Urban Health Initiative grant. The department also uses it as a family practice center, as well as for teaching students and training residents in family practice.

Residencies in family practice were started on July 1, 1979. In addition to their experience in the family practice center they will receive training at Washoe Medical Center and the Veterans Administration Medical Center. It is a three-year program with six residents in the first year, two in the second and two in the third.

Pediatrics

The pediatric residency program under the supervision of Dr. Burt Dudding, chairman of the Department of Pediatrics, is a three-year program at Washoe Medical Center, designed to qualify residents for certification by the American Board of Pediatrics. There are four residents planned for each of the three years of the program.

Surgery

Dr. Ralph DePalma, newly selected chairman of the Department of Surgery, is planning a surgical residency program anticipated to begin in 1981 at the Veterans Administration Medical Center in Reno and Southern Nevada Memorial Hospital in Las Vegas, with probable affiliation with other community hospitals to be determined at a later date. This plan will cover both northern and southern Nevada.

Obstetrics and Gynecology

According to Dr. George Furman, chairman of the Department of Obstetrics and Gynecology, proceedings are underway to initiate residencies in obstetrics and gynecology in 1981. These will be carried out at Southern Nevada Memorial Hospital in Las Vegas, with some emphasis on intensive neonatal care given through a center at Sunrise Hospital in Las Vegas.

Student Affairs

Dr. Owen Peck, associate dean for student affairs, has noted that the conversion has doubled the number of students, which immediately placed an increased burden on financial aid resources. Fortunately, with the decrease in federal loans, private citizens and voluntary organizations have come to the aid of financially distressed medical students. The Fred M. Anderson Scholarship endowment, which was established by the medical students as their contribution toward future students, has had donations from many Nevadans, particularly physicians. In 1980 a $622,000 gift was given by the Hubert McCoskey family to the medical school for a medical student scholarship endowment. The Nevada Division of the American Cancer Society has also established an annual scholarship, initiated by William P. Barry of Las

Vegas. In 1981 this will be increased to 18 scholarships for medical students in need. Many other donors are giving annual scholarships as well.

Administration Changes and Faculty Recruitment

George Smith, MD, a strong influence in the development of the medical school, and its first dean, resigned in November 1977 to assume the position of professor of pathology and director of the Veterans Administration Southeastern Regional Medical Education Center at the University of Alabama in Birmingham. He was succeeded by Dean Thomas Scully, MD, who had served as associate dean under him in Nevada. Dr. Scully carried through the negotiations among the regents, legislature and liaison committee that led to the conversion to a four-year school. Unfortunately, prolonged illness and an operation caused him to resign as dean in October 1979, when he assumed a less demanding role as professor of pediatrics.

Ernest Mazzaferri, MD, an outstanding endocrinologist who had been recruited as chairman of the Department of Medicine from Ohio State University was selected in October 1979 to serve as acting dean. He has very ably carried out the completion of the conversion, initiating residency programs, recruiting clinical faculty and solving the thousands of problems of a neophyte four-year school. As Dr. Mazzaferri accepted the deanship only temporarily, Dr. Robert Daughtery, associate dean of the Indiana University School of Medicine was recently selected as dean of the University of Nevada, Reno, School of Medicine. Dr. Daughtery is a nationally recognized educator with command expertise in administration of medicine. He brings to Nevada enthusiasm, knowledge and experience which will serve the school of medicine well.

Continuing Medical Education

In 1973 the school of medicine was accredited by the American Medical Association to sponsor continuing medical education (CME) programs throughout Nevada. It became apparent in 1974 that the best way to carry out such a program was to form a joint committee with the Nevada State Medical Association. This made it possible for the Nevada State Medical Association, with its organizational abilities and many specialists, and the UNR School of Medicine, with its consultation and research abilities, to work together towards a common end. Most members of the Joint Committee on Continuing Medical Education are practicing physicians, including representatives from the rural areas. It is now possible for most physicians throughout the state to meet the requirements for certification of the AMA Physician's Recognition Award without leaving their community. The Nevada State Legislature has passed a mandatory CME law (recertification) which will probably be implemented by the Board of Medical Examiners in January 1981.

Rural Health

Throughout the development of the school there has always been a strong commitment to respond actively to the health needs of rural Nevada. To accomplish this, in 1978 Dean George Smith appointed Dr. DeWitt C. Baldwin, Jr, to the position of assistant dean for rural health and authorized creation of the Office of Rural Health. In early 1979 the school received a grant of $400,000 from the Robert Wood Johnson Foundation to undertake a broad program of activities designed to improve health care delivery to the rural areas of Nevada.

The objectives of the new office fell into two areas (1) rural health manpower recruitment and retention and (2) the creation of a statewide liaison, communication and information system in rural health. The first set of activities included: recruiting and retaining physicians and other health professionals, establishing a liaison with the National Health Service Corps, developing a clinical field faculty network, arranging for rural preceptorships for medical students and primary care residents, developing a medical consultation program for rural health professionals, and assessing and developing programs to meet the CME needs of providers of rural health care.

The Office of Rural Health represents a clear interface with the health care system throughout the state, particularly in rural areas, and clearly demonstrates the commitment of the school to rural health. An example of the latter was the appointment of more than 40 physicians from rural areas in Nevada to clinical faculty positions during the past year, and the assignment of all 36 senior students to required month-long rotations in 12 of the state's rural communities.

An as yet unassessed factor of great importance to the rural areas of Nevada and Utah may be the potential impact of the MX missile system, which could double the populations of many rural com-

Figure 2.—The University of Nevada, Reno, School of Medicine, with the Sierra Nevada Mountains in the background.

munities in these two states. It is obvious that the influx of new people to construction sites and later to operational points would create massive dislocations, as well as pressures on existing health, social and educational services within these communities. Public health issues such as water supply, sewage disposal, environmental protection, housing and transportation, would emerge as new and important problems for these rural communities and the physicians who practice in them.

Nevada's state medical school must continue to be responsive to the intent of the legislature in caring for the state's changing communities, both urban and rural. It is preparing for this challenge.

Acting Dean Mazzaferri believes that the future of the University of Nevada, Reno, School of Medicine looks bright. The medical school as it exists today is shown in Figure 2. In the spring of 1981 ground will be broken for a new 5 million dollar research building. A new ambulatory patient research and education building to cost 6 million dollars is in the planning stages and established investigators and educators, as well as young, promising new faculty continue to join the ranks of the school. Dr. Mazzaferri states,

> We look to develop a small, educationally superior school of medicine, which by strong affiliation and interchange with the community, will educate students according to the highest standards in medicine, so they will be prepared to go to residencies in whatever field of specialty they choose.

Refer to: Veith I: Changing concepts of health care: An historian's view (Medicine in Perspective). West J Med 133: 532-538, Dec 1980

Changing Concepts of Health Care: An Historian's View

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WITHIN THE RECENT PAST such expressions as *health care,* or even *health care delivery,* have come to supplant the traditional term *medicine.* In essence, their meanings are identical. From the beginning of man's concern with healing, the practice of medicine was expected to fulfill a threefold task: the treatment of disease, the cure of disease and, finally, the prevention of disease.

It is, of course, an audacious undertaking to attempt to compress into one essay the changes and permutations that concepts of health care have undergone in the course of documented medical history.

Medical historians often have been criticized for being too much concerned with the achievements and biographies of renowned individual physicians, rather than with the medical care actually given to mankind by their contemporaries, by all physicians, be they celebrated or more or less anonymous. To live up to the title of my essay I will try to refrain from any medical hero worship—although an occasional name may not be avoidable—and, rather, discuss the practice of medicine as it has changed throughout the ages.

Because of the renewed prominence of King Tutankhamen, I will begin with a mention of how medicine was practiced in the Egypt of his day. Even though we think of medical specialties as a modern phenomenon, some specialization had begun in ancient Egypt. Also, medical treatment was not dispensed uniformly, but was given only to those whose illnesses were judged by the healer to be curable. In fact, the most important of all Egyptian medical papyri (the *Edwin Smith Surgical Papyrus*) allowed a physician to pronounce one of three verdicts after examining a patient: (1) "This is an illness which I will treat," (2) "This is an illness with which I will contend," (that is, I will maintain an expectant attitude) and (3) "This is an illness which I will not treat."[1]

This apparently cold-blooded evaluation of whether a patient's condition was treatable was derived from the nature of medical status and practice in antiquity. Rather than being settled in one locality, physicians led the lives of itinerant craftsmen and, like them, depended for their livelihood on the esteem they had earned on previous visits. With a record of many successful cures they usually enjoyed a reputation of wise judgment and therapeutic skill, which attracted more and more patients.

This method was also adopted by the ancient Greek physicians who felt no twinge of conscience if they declined treatment of terminally ill patients. The Hippocratic oath, which is so often cited, and misquoted, does not make any demands that doctors be samaritans. However, physicians were instructed in the writings of Hippocrates to adjust their fees to the economic condition of patients and to forgo payment altogether if the patient was a stranger in town and poverty-stricken. Moreover, physicians were urged to seek consultation from colleagues.

In ancient China the custom of consultation—that is, the seeking of a second opinion—was carried out to what might seem an inconceivable

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Adapted from a lecture presented at the Sixth National Seminar of the Vista Hill Foundation, Coronado, California, February 15, 1980.

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extreme to modern physicians. In the case of illness in a family, not one but several physicians were called in. Each made his diagnosis and made a suggestion about therapy. The patient and the family would then select the doctor who had announced the most agreeable diagnosis and treatment. He was retained and all the others dismissed. It is noteworthy that Chinese physicians also were inclined to prefer those patients whose conditions appeared curable. This approach to medicine persisted throughout the millennia of Chinese medical history and well into the 20th century.

With the rise of Christianity in the West and Buddhism in the East, priests, who functioned as healers, were no longer permitted to make selections from among patients. They were expected to treat all comers, regardless of the severity of an illness.

In Europe, together with religious medical practitioners there were numerous lay physicians who were under the strict control of local authorities concerning the nature of their medical practice, including their successes and failures. In fact, malpractice became a serious matter; severe financial and even physical penalties were meted out by the courts to those physicians who had caused injuries or aggravation of the original illness through carelessness or lack of knowledge.

In contrast to clerical physicians who were expected to extend equal care to all who sought their help and healing, lay physicians, even though they might have been expected to do likewise, left records of their discrimination between wealthy and poor patients. The difference made by them between the rich and the poor was not confined to the amount of personal attention given but extended to the type and value of medications they gave to their patients. This was a time when physicians often were also pharmacists, making and dispensing the drugs they prescribed. In fact, the dual activity of doctor and apothecary persisted in England until 1511, when King Henry VIII introduced a change after condemning this joint practice:

> The science and cunning of Physick (pharmacy and medicine) and surgery . . . is daily within this Realm exercised by a great multitude of ignorant persons of whom the greater part have no manner of insight in the same, nor any other kind of learning.[2,3]

King Henry went on to state that some of the so-called physicians were totally illiterate just like common artisans, such as blacksmiths, weavers and women (midwives?), and that they took upon themselves great cures, in which they applied sorcery and witchcraft, as well as medicines for diseases, even noxious medicines, such as had never been used before. All this was perpetrated "To the great displeasure of God, the great infamy to the Faculty [of medicine], so that the people cannot discern the unlearned from the learned physician."

After having proclaimed this sorry and dangerous state of affairs, King Henry decreed that the practice of medicine was to depend on a doctor's having passed an examination by the Dean of St. Paul's Cathedral and four "doctors of Physick," and at least one expert surgeon. Moreover, the physicians were strictly forbidden to act as pharmacists.

Whether these lines were written by Henry VIII, or by an anonymous courtier, we will never know. However, they will always be attributed to the king because it was he who instituted a thorough reform in the practice of medicine and introduced an examination system that was, and has remained, the sine qua non of medical licensure.

At any rate, it is evident that Henry VIII was anxious to weed out from among the so-called physicians the many "Smiths, Weavers, Charlatans, and wise Women," all of whom had pretensions of being learned healers, whereas it was believed that they used sorcery and witchcraft and untried medicines.

But, to return to those doctors who discriminated in their prescriptions between rich and poor, and dispensed medication as well as their medical advice, I must mention John of Gaddesden (13th century) who served Chaucer as his model for the Doctor of Physick in the *Canterbury Tales*. John of Gaddesden was the author of a work entitled *Rosa Anglica* (first printed in Paris in 1492), in which he listed a number of precious stones and pearls that, finely ground, were to serve as medication for the rich, while to the poor he dispensed roots and herbs that could be easily and cheaply obtained by anyone. Such distinctions were made without the slightest embarrassment on the part of a doctor, but simply because God had willed that some patients were rich while others were poor, and that doctors were entitled to a comfortable livelihood which was most easily ensured by wealthy patients.

Many of the diseases that today are the most long-drawn-out, painful and deadly ones (such as

some cardiovascular disturbances and types of carcinoma) have come into existence only in the recent past. In previous centuries, when people rarely lived past the age of 50, many disorders of the heart and circulation rarely had a chance to make themselves felt because people had succumbed to other, now curable and preventable, diseases. Senile dementia, or other aspects of aging, rarely developed because the life span was too brief.

For this reason, as well as because of the disinterest of the medical profession in the aged, geriatric medicine as a discipline did not come into being until the first decade of this century. After all, until recently the dread of aging that is still felt by many of us today was fortified by the Bible, doubtless the most influential and widely known literature for nearly 2,000 years. A pertinent passage from Ecclesiastes (12:1-2) (KJV) illustrates the irreversibility of age and the process of aging, and with it the gradual desocialization of the person so afflicted:

> Remember now thy Creator in the days of thy Youth, while the evil days come not, nor the years draw nigh when thou shalt say, I have no pleasure in them;
> 2. While the sun or the light, or the moon, or the stars, be not darkened, nor the clouds return after the rain;

Further on, the biblical text refers not only to the dimming of vision, but also to the impairment of hearing, when the song of birds, the laughter of youth and the sound of music become low and scarcely audible. Another sign of age, according to Ecclesiastes, is the fear of altitude as well as general fears, all of which impede the enjoyment of life.

In contrast to the pessimistic attitude of the biblical writer in Ecclesiates in Cicero's *De Senectute* (44 BC), which defends the aged and aging. When Cicero wrote this work he was 63 years old, an exceptional age for that time. He said, "Above all, when you wish to read or hear history, you will find that many of the biggest countries have been unsettled and endangered by youths, while they are being strengthened and supported by old men."[4] Cicero's idea of the value of age was also held by the Roman statesman Seneca, who advocated the value of gerontology—the care and attention for man in advanced age—when he suggested to his fellow Romans that they use extreme care to maintain health, so as to prevent its breakdown; we must fight against the collapse of health as if it were against a specific illness.

Because aging and geriatric medicine are sidelines of my survey of changing concepts of health care, I will omit authors in the intervening years and quote the 19th century philosopher and poet Friedrich Wilhelm Nietzsche, an unrelenting opponent of human weakness. With absolute realism he said, "The meaning of life implies cruelty and unforgiving opposition against everything that is weak and old in us"; and rather than speaking of the accumulated and valuable wisdom of age, Nietzsche said of himself, "It is true I am aging, but every day I am learning something new."[5]

As man's life span has continued to lengthen, the physical and emotional problems of aging have occupied more and more space in medical writings. After centuries of near total indifference towards such problems, there arose in the 17th and 18th centuries a sudden flurry of publications that announced ways and means of attaining a healthful old age. The common theory of most of these writings was that aging and death were due to a loss of human warmth. To supplement this diminishing body heat, young boys or girls were placed into the bed of aging persons in the hope that their body warmth and breath of life would strengthen the elderly patients.

Like many bits of folk wisdom, this practice had its origin in the Bible, in the First Book of the Kings (1:1-3) (KJV):

> Now king David was old and stricken in years; and they covered him with clothes, but he gat no heat.
> 2. Wherefore his servants said unto him, Let there be sought for my lord the king a young virgin and let her stand before the king, and let her cherish him, and let her lie in thy bosom, that my lord the king may get heat.
> 3. So they sought for a fair damsel . . . and brought her to the king.

Unfortunately, so the Bible tells us, this attempt at physical transference of youthful warmth failed to arouse in the aged King David the sexual desire to possess the fair maiden, or the will to live. Even though this biblical story cannot help but remind us of the studies of Masters and Johnson, it also awakens memories of the Nazi concentration camp experiments in which persons intentionally exposed to near fatal hypothermia were revived by being bedded together with warm female inmates—not necessarily young and fair maidens—to find out whether human warmth and vitality could be transferred to a near-frozen and weakened person from a normal, warm and healthy bedmate.

But, to return from the frightening combination of King David's biblical death and the experiments

of Hitler's concentration camps, I must mention the great 18th century physician Christoph Wilhelm Hufeland. His work *Macrobiotic, or the Art of Prolonging Human Life* has become the classic example of what we might call "gerophylaxis," which in spite of its scientific content did not contain any secret method of attaining healthy longevity, even though medicines fashioned of gold and ginseng *(Panax schinseng)* were used by many patients in addition to Hufeland's recommendations.

If health care, as we know it today, is concerned with the aging process and the innovation of geriatric medicine, it has also become enriched, in the course of millennia, with a concern for the health of children. For many centuries children were treated, not only in medicine but also in art, literature and dress, like miniature adults with the same needs and ailments. Hence, as a result of the Industrial Revolution, when there was an unlimited demand for skilled and unskilled workers, children became a ruthlessly exploited part of the labor force. And until this century physicians gave no warning of the irreversible damage thus inflicted upon these young bodies and minds.

In 1923 the International Society for the Help of Children created the "Geneva Declaration of the Rights of Children." This declaration has several postulates that attempted to liberate children, presumably forever, from their unfortunate and unhealthful state as miniature adults. In paraphrase some of the postulates read as follows: (1) Each child is to be offered the opportunity of a regular bodily and mental development. (2) In times of economic exigency, the needs of the child are to be considered in preference to those of the adults, as it is the child that carries the future of humanity. (3) The child should receive help without consideration of race, nationality or religion. (4) The starving child should be fed, the sick child should be cared for, the retarded child should be educated, the lost and the deserted child and the orphans should be protected. (5) In work the child should be protected against any exploitation.

With these principles it is scarcely to be wondered at that gradually a separate specialty of medicine, geared to the health care of children, came into being and spread widely. As with geriatric medicine, it was but part of the ever-increasing trend towards medical specialization in modern times.

It is interesting that in the history of medical specialization, psychiatry was recognized very late. Health care of psychiatric patients was systematically begun only in the 19th century. Until that time the medical world had undergone many changes of thought in trying to understand mental disease. Mental disease had been understood and intelligently treated in Greco-Roman antiquity, but, with the impact of the Middle Ages, behavioral aberrations became associated with witchcraft and the devil. Not uncommonly, treatment was carried out by the Inquisition, often with a deadly result for the patient. So, there was a hiatus of nearly two millennia before psychiatry reached the eminence it had in Greek and Roman times. Moreover, within the last decades, psychiatric problems have arisen that are quite outside the traditional framework of Judeo-Christian thought.

Because death, suicide and euthanasia are telling examples of concern in a changing society, I will mention some of the attitudes that have been held on these subjects. Death, to begin with, has become a matter that is openly discussed. This phenomenon is, of course, almost entirely the result of modern concepts of psychiatry, in particular, those held by Elisabeth Kübler-Ross. She was one of the first, if not the first, to make known her studies on the reactions of patients who had been told of their impending death.

Only a few years before Kübler-Ross' epoch-making publications on death and dying, I published a brief historical essay entitled "Should the Patient be Told?"[6] In that essay I examined the opinions of many physicians of the past, mostly surgeons, as to whether a patient should be told if he had an incurable illness. I found that the answer invariably was negative.

An outstanding Italian physician and surgeon of the pre-Renaissance times, William of Salicet—speaking with an equal authority as a physician and a surgeon—was keenly aware of the role played by psychic influences in the recovery from disease or operation:

> Those who practice this art (medicine) should . . . acquiesce to the wishes of the patients and conform to them, (if they do not in any way wish to result in disadvantage to his operations) and comfort the patient by gentle actions, soft words, agreeable and proper, and promise him cure in all cases, even though they are hopeless; and the operating physician himself (must) remain convinced that there is a chance for health in such an infirmity. . . . For the mind of the patient derives from such discourse and promises, a secret influence and a great disposition by which nature acquires vigor and

resistance against the disease. That is why there will result an action far more powerful than that which can be produced by all the efforts of the physician, with his instruments and even his medicine, an action such that it routs the illness. But, it is necessary that the doctor discuss the condition of the illness with the friends or the relatives of the patient . . . lest the friends might not find themselves prepared against all cruel disillusion, and so that, if the patient should die, one could not say that the doctor has caused the death, but speak well of his recovery, if the patient is cured.[7]

Faith in the curative powers of the mind, so ably expressed by William of Salicet, had, indeed, been part of medical belief since its inception. Hippocrates expressed it succinctly: "Where there is love of man, there is also love of the art. For some patients, though conscious that their condition is perilous, recover their health simply through their contentment with the goodness of the physician."[8]

The ideas of Hippocrates and Salicet, in turn, were passed on to successors who paraphrased the original words and added their own thoughts of encouragement for patients. Lanfranc, the acknowledged founder of French surgery, wrote in the early 14th century: "Give the surgeon no counsel unless he be asked; let him not speak with any woman in folly in the sick man's house; nor chide with the sick man, and in all manner of sickness promise him cure, though he despaired of him, but never say the latter to his friends, but tell them how it stands."[9]

In the 15th century a German wound surgeon, Hieronymous Brunschwig, stated that a surgeon "should not say too much except to promise health to the patients . . . he should speak to the sick and wounded chastely and gently and always promise them recovery. But, to their friends he should tell the truth and hide nothing."[10]

It was Henry de Mondeville, a famous French surgeon, who expanded the brief statements of his predecessors almost to the point of the ridiculous. His views on the subject are so refreshing and so much at variance with ours today that in his sly humor we can detect a bit of irony: The surgeon should regulate the entire regimen of the patient with a view to pleasure and joy promising him a rapid recovery. The patient is led to believe "that once cured, he will perform, single-handedly, great wonders, that he will be promoted to the highest positions in his field of work."[11]

It is obvious that the primary reason the early physicians advised the withholding of dire prognoses from patients was different from that advanced today. Although not unmindful of the mental anguish suffered by patients with incurable disease, and wishing to assuage it, the earlier physicians were chiefly concerned with the "possibility of unexpected cure that might result from a confident and trusting mind."

What a difference between comforting a patient with personal fairy tales that promised fulfillment of all his wishes and Kübler-Ross' realistic insistence on a patient's duty to cope with the truth by going through five precisely defined emotional stages: (1) denial and isolation, (2) anger. (3) bargaining, (4) depression and, finally, (5) acceptance. Throughout it all, however, Kübler-Ross realized that the patients never abandoned hope; nor did she deprive them of this last hold on life.

From Kübler-Ross' beliefs it is not too great a step to the views of one of America's most distinguished physicians, Franz Ingelfinger, a celebrated internist and former editor of the *New England Journal of Medicine* who died in 1980. He stated that "the responsible physician, through whom diagnosis and treatment are channeled, must—and I emphasize *must*—take time to explain his impressions and recommendations to the patient. A crucial condition, moreover, is that the doctor use terms that the patient can understand . . . and language that is distinctly non-authoritarian."[12]

In comparing Kübler-Ross' and Ingelfinger's writings with those of the past, I am arrested by another pronounced difference between the older texts and today's practices: the patient is invariably referred to with a masculine pronoun. Although this is partly a matter of linguistics, it probably also indicates that neither surgeons nor physicians had much experience with female patients. However, Hieronymous Brunschwig, mentioned above, was the author of a general textbook of surgery, in which he described and illustrated the operation of mastectomy for the treatment of carcinoma of the breast. Apart from mastectomies and operations for hernia, treatment of female patients, just as of women in labor, was left to the skills of midwives or other "wise women" who abounded in all communities.

From the traditional and modern medical attitudes towards hopelessly ill patients it is but a short step to the concept of euthanasia and medicine's thinking about it. Initially, I must stress that in this subject the Hippocratic oath has a firm and negative opinion, which thus far has been respected and adhered to by the medical profes-

sion. "I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrongdoing." From this is derived the well-known injunction *primum nil nocere* (first of all do no harm), that every physician learns in medical school. In regard to euthanasia, one version of the oath continues, "Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course." Next, occurs an injunction against carrying out abortions.

Perhaps the most telling examples of the evolution of health care in society are the changes in attitude toward these injunctions against helping patients to die and assisting at abortion. Judeo-Christian society has always considered these to be weighty admonitions, though they were by no means representative of Greek ideals and conduct. Quite to the contrary, abortions were carried out and with medical initiative. The help of patients to die was not only given, but often expected by Greek society of physicians when confronted with a terminally ill patient. The reason for this last-named practice is given in Plato's immortal work *The Republic,* which contains provision for a supreme governmental paternalism that would dictate human affairs, including the choice of marriage partners, the number of offspring and the education of children. As to the need for medical care, Plato believed that illness was a sign of decadence and personal degeneration, brought on by the decay and permissiveness of Greek society and government. In Plato's opinion it was the duty of the wellborn to keep themselves in good health and to be sufficiently well educated to provide hygienic regimens and medical care for themselves and the members of their households. Those of the aristocracy who, of themselves, failed to achieve freedom from illness were to be considered unworthy of medical treatment and should be permitted to struggle along or die as circumstances dictated.

In all of his writings Plato reflected the belief, traditional to most societies, that mankind's mode of life in a past golden age, when simplicity and naturalness prevailed, had been wiser and much more healthful than in later times; hence, the need for medical treatment resulted from decadence caused by the complexities of civilization.

If physicians refrained from the treatment of all diseases felt to be self-induced, as Plato idealistically urged, this should not imply that they were lacking in humanity, but simply that they pragmatically refrained from treating those whom they deemed incurable. For it was considered inhumane to prolong the suffering of the dying. Today this may sound unfeeling and cruel to some, but, in Platonic thought, not only the refusal of treatment but actual euthanasia was considered permissible and entirely proper.

The treatment discussed above was only given to the moneyed classes of society, of course. With the common people the situation was different. They depended for their livelihood on their ability to work; more important, their work was essential to the welfare of the community. In Plato's own words:

> When a carpenter is ill he asks the physician for a rough and ready cure: an emetic, or a purge, or a cautery or the knife—these are his remedies. And if someone prescribes for him a course of dietetics and tells him that he must swaddle his head, and all that sort of thing, he replies that he has no time to be ill and he sees no good in a life which is spent in nursing a disease to the neglect of the patient's customary employment; and therefore dismissing a physician who condones this disease-caused indolence, the patient resumes his ordinary habits and either gets well and lives, and does his business, or—if his constitution fails—he dies and has no more trouble.[13]

In all its ramifications, Plato's *Republic* remained centered on his main theme, namely, that the overriding needs of society and the requirements of the ideal state take precedence over those of individual citizens. Plato did not sympathize with individual persons: he believed they had to subordinate their own desires and needs to those of the majority. Even a timely death after lingering illness was part of the fundamental obligation of citizenship in the ancient Greek states.

Much later, Plato's views were shared and emulated by Sir Thomas More (Saint Thomas More), the great Catholic humanitarian and "man for all seasons," who served in the court of Henry VIII. He was knighted by the monarch, and later sainted for his martyrdom when he opposed the first divorce in Catholic royal history. Immortal for his authorship of *Utopia,* More advocated that those who were very sick must be supplied with all the care, kindness and drugs that were available.

> But if a disease is not only beyond treatment, but also a constant source of pain and agony, the priest and magistrates are to remind the patient that he is not up to all the tasks of life, is troublesome to others and a burden to himself and is in fact, "outliving his own death." They advise him not to go on feeding that pestilence and sickness any longer, nor to hesitate to die, since life is a torment to him. They bid him to take good hope and release himself from that bitter life, as if from a prison or a torture rack, or at least give his permission for others to remove him. They tell the patient that

putting an end to his suffering would be well and proper; and since in that matter he will be taking the advice of priests, the interpreters of God, his action will be pious and holy.[14(vol2.p88)]

To us in the 20th century, More's words may convey a remarkable insight for a man so deeply steeped in Christian philosophy, yet they present an attitude totally at variance with the general beliefs of his church, which abhors suicide for any reason. But, then, More's utopian attitudes towards other medical problems, such as care of mental patients, were equally unrealistic and in sharp contrast to the practices of his contemporaries in England. Far from being treated as "lovable fools," as More saw them, mentally ill patients were incarcerated and flogged in Bedlam.

We have received the verdicts of Plato, one of the wisest men of the past, and Thomas More, one of the saintliest men, which indicate that social change has often demanded a merciful end for incurably ill patients who are no longer productive in society. If Plato and More could have envisaged machines that artificially pump breath and nourishment into a comatose patient, their recommendation would doubtless have been to put an end to such an existence.

In spite of the lack of realism in More's views on the treatment of the insane, a passage from his *Utopia* seems pertinent:

The Utopians take great delight in fools. Although it is considered shameful to do them any harm, yet it is permissible to get pleasure from their foolishness. For the Utopians think that this is very good for the fools themselves. If anyone is so stern and severe that he cannot laugh at any word and action of theirs, to his safekeeping (the Utopians) refuse to entrust a fool. For they are afraid that a man who finds no use and no amusement in a fool (and this is a fool's only advantage) will not look after him with sufficient kindness.[14]

In a similar vein, More's *Utopia* continued, "To mock a man who is deformed or crippled is considered disgusting and disgraceful, not to the man mocked, but to the mocker. For he stupidly reproaches as a failing something that the patient could not possibly avoid."

Although Thomas More shared Plato's pragmatism concerning the final dispositions of patients who were incurably ill and forever unable to carry out their duties to the state, he proposed care and compassion for the insane and crippled, even though they too would never fulfill the tasks of citizenship. From that time on, until the few dreadful years of the Thousand Year Reich of the German Nazis, the question of euthanasia, even in the form of mercy killing, never arose again on a large scale. Physicians did their utmost to return to the primary principle of Hippocrates' *primum nil nocere,* to the extent of not only transfusing blood but of transplanting organs, in the hope of postponing death rather than avoiding it.

Even in so brief a discussion of the history of health care, it is evident that concepts rarely persist very long and that none of them ever remains unchallenged. Thus, even psychiatry, which deals with the psyche, the intangible soul itself, is not left unshaken in its adherence to a belief in curability. Recent events in drug therapy have brought the study and treatment of the soul into the realm of biochemistry.

As an historian, I cannot project the history of health care into the future. As a scholar, I cannot venture to guess what concepts of medical care are yet to arise. It is certain, however, that even our increasing knowledge of individual diseases and discovery of new disease entities will not end the quest for the ultimate concepts of ideal health care.

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Prescribing Narcotics to Habitual and Addicted Narcotic Users

Medical and Legal Guidelines in California and Some Other Western States

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Confusion exists among physicians over the legal requirements and appropriate prescribing of narcotics to addicted or habitual users of narcotics. The result has often been either (1) the deprivation of appropriate treatment for patients who desire detoxification or adequate pain relief, or (2) illegal prescribing by physicians. Because most narcotics are potent and dangerous substances, certain legal restrictions are necessary to protect the general public. State-approved programs have been established to prescribe methadone and propoxyphene napsylate for addiction treatment. Current laws and regulations in California permit every practicing physician to provide effective and safe treatment for addiction and pain relief.

FIFTEEN YEARS AGO, a Presidential Advisory Commission expressed concern that practicing physicians were confused over when narcotic drugs could be prescribed to drug addicts.[1] The Commission found that in most instances doctors shunned addicts as patients. The intervening years have seen little improvement in this situation. In California the confusion is exacerbated by a legal maze of statutory provisions that frequently seem to contradict each other. Medical and legal guidelines for prescribing narcotics to habitual and addicted narcotic users are summarized below. Some reported cases in which physicians have been disciplined for illegal prescribing are reviewed, and acceptable medical regimens are outlined to guide physicians in prescribing drugs to narcotic users for pain relief, detoxification or withdrawal, and medical maintenance.

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Restrictions on Prescribing Narcotics to Addicts and Habitual Users

If a patient is an addict or habitual user, or represents himself as such, the California Health and Safety Code permits a physician to prescribe, administer or dispense controlled substances only under the following conditions: (1) emergency treatment; (2) when the patient's addiction is complicated by the presence of incurable disease, serious accident or injury, or the infirmities of old age; or (3) in treatment of addiction which com-

plies with provisions of the California Uniform Controlled Substances Act, such as methadone programs approved by California's Research Advisory Panel.

The exceptions listed above form the basis of legal and medically appropriate prescribing for pain, detoxification and medical maintenance therapy. Table 1 summarizes prescribing restrictions for some of the common narcotics.

Emergency Pain Relief

The California Uniform Controlled Substances Act permits a physician to administer emergency treatment with controlled substances to an addict or habitual user of narcotics. A recently passed bill by the legislature (AB 2378) authorizes a physician to directly dispense a 72-hour supply of narcotics for pain purposes only whenever the patient is not expected to require additional amounts beyond this time period. Thus, the doctor who administers narcotics or other controlled substances to an accident victim has nothing to fear if it later turns out the victim is an addict. The exception even allows temporary administration of controlled substances to an addict in the stages of acute withdrawal, although it should be a one-time, one-dose treatment while the addict awaits more definitive care. In the case of *People vs Anderson* (29 Cal App 3d 551, 1972) a physician was charged with six counts of improperly issuing prescriptions to narcotic addicts. His defense was that he gave each of the six addicts a prescription for 10 mg of methadone (Dolophine) to be taken four times a day for four days, simply as emergency treatment until they could be admitted to a drug treatment program. Each of the prescriptions stated, "Take as directed and immediately cut down and immediately report to a Drug Abuse Center as arranged." Nonetheless, a conviction was upheld on the basis of expert testimony presented by the prosecution that no true medical emergency was present because none of the six patients was suffering from any acute withdrawal symptoms at the time he was in the defendant's office. Even the prosecution expert agreed, however, that

> it was proper for a doctor to give an addict a prescription for one or two doses of methadone if the addict was on his way to the hospital. The prescription, however, should last just long enough for the addict to get to the hospital, instead of the four days involved in each of the six orders here involved.

If any drugs listed on Schedule II of the California Uniform Controlled Substances Act are prescribed to a habitual user of narcotics, however, even for emergency pain relief, the California Health and Safety Code requires that a report be filed with the attorney general containing the name and address of the patient, the character of the injury or ailment, and the quantity and kind of controlled substance used (Table 1). In California, the attorney general's office provides a convenient registration card for physicians which can be obtained by contacting his office. Three points should be noted with respect to this requirement. First, the term "habitual user," as used in the law requiring a report, has been held unconstitutionally vague, except as applied to addicts, in the decision of *McCurty vs Board of Medical Examiners* (180 Cal App 2d 760, 1960). Thus, even though prescriptions to habitual users may be subject to the same limitations as addicts, the reporting requirement applies only to addicts. Some physicians, however, choose to register all habitual users of Schedule II substances, including hyperactive children for whom methylphenidate (Ritalin) is prescribed. Unnecessary or over-registration is, therefore, apparently preferred to under-registration to avoid any possible penalty. Second, the reporting requirement only includes drugs that are prescribed or furnished. Therefore, if an addict desires a Schedule II narcotic for pain relief while attending an emergency room, clinic or physician's office, and the physician issues a prescription for a Schedule II controlled substance, he must register the addict with the attorney general's office. If emergency Schedule II narcotics are administered, however, in a physician's office or hospital emergency room, a report need not be filed. Third, the Schedule II referred to is in the California Controlled Substances Schedule, and not the federal schedule. There are some significant differences. For example, barbiturates and methaqualone remain on Schedule III in California, while federal authorities have moved them to Schedule II. Thus, such prescriptions for these drugs would not have to be reported.

Nonemergency Pain Relief

Chronic pain may be treated with any narcotic chosen by the physician because the California Health and Safety Code permits a physician to prescribe "where the patient's addiction is complicated by the presence of incurable disease, serious accident or injury, or the infirmities of old

age." This situation includes terminal cancer, a neuromuscular disorder, arthritis, angina pectoris or other disease that may produce chronic, severe pain and require administration of narcotics even to the point of addiction. Physicians' confusion over this issue often deprives patients of humane treatment in relieving pain.[2,3] In addition, physicians may frequently withhold proper relief from addicts, because they erroneously assume an addict's regular narcotic dose will relieve the pain of accident, injury or disease. This is not the case, however, because addiction essentially eliminates the pain-relieving ability of an addict's regular maintenance dose. For this reason, addicts generally should be prescribed narcotics and other analgesic drugs in regular dosage for an accident, injury, illness or surgical procedure.[4] Several examples of the application of the legal right of physicians to prescribe the chronic use of narcotics for pain relief to narcotic addicts can be found in the decision of *Moran vs Board of Medical Examiners* (32 Cal 2d 301, 1948). Dr. Moran was charged with prescribing narcotics for three addicts. In each case, the court found the prescriptions were justified by the presence of an incurable disease. The first case involved a female addict complaining of severe pain in the left side of her face resulting from trifacial neuralgia. He injected her face with novacaine and alcohol, and on 18 different dates within two months, prescribed morphine sulphate for the pain. He discontinued treatment when the woman refused to enter a hospital after he had arranged for treatment of her addiction. The second case involved a male addict who was choking from an acute asthmatic attack. The doctor tried epinephrine, and when that did not work, administered vitamin C and morphine, which controlled the choking. He then prescribed morphine sulphate on nine occasions within a month. The third case was a

TABLE 1.—*California Restrictions on Some Common Narcotics When Prescribed for Addicts and Habitual Users*

	May Administer for Emergency Pain Relief Without Registration	*May Prescribe or Furnish for Pain Relief and Must Register Addict or Habitue*	*May Prescribe for Pain Relief and No Registration Required*	*May Prescribe for Detoxification in State-County Hospital, Jail, or Approved Facility if Addict or Habitue Registered*	*Formal Mechanism Established for State Approval to Use for Detoxification and Maintenance Treatments*
Schedule II					
Codeine	Yes	Yes	N/A	Yes	No
Morphine	Yes	Yes	N/A	Yes	No
Meperidine (Demerol)	Yes	Yes	N/A	Yes	No
Hydromorphone (Dilaudid)	Yes	Yes	N/A	Yes	No
Oxycodone (Percodan)	Yes	Yes	N/A	Yes	No
Opium extracts (Pantopon)	Yes	Yes	N/A	Yes	No
Hydrocodone	Yes	Yes	N/A	Yes	No
Methadone (Dolophine)	Yes	Yes	N/A	Yes	Yes
Schedule III					
Codeine mixtures (Empirin, Ascodeen)	Yes	N/A	Yes	No	No
Hydrocodone cough mixtures (Hycodan, Citra Forte, Tussend)	N/A	N/A	N/A	No	No
Scheduled IV					
N/A					
Schedule V					
Codeine mixtures (Actifed-C, Robitussin A-C)	N/A	N/A	N/A	No	No
Unscheduled					
Propoxyphene hydrochloride (Darvon)	Yes	N/A	Yes	No	No
Propoxyphene napsylate (Darvon-N)	Yes	N/A	Yes	No	Yes
Pentazocine (Talwin)	Yes	N/A	Yes	No	No

N/A = not applicable

patient afflicted with spinal arthritis, for whom Dr. Moran prescribed opium extracts (Pantopon) on two occasions for pain.

It is highly recommended that a physician initially attempt treatments other than use of narcotics before a diagnosis of incurable disease is made. This should be carefully documented in the patient's chart, because the physician must bear the burden of proving a claim of incurable disease for which narcotics are the only treatment. In the case of *People vs Lawrence* (198 Cal App 2d 54, 1961), a court held that the doctor had failed to prove that narcotics were necessary in a case where he prescribed 20 grains of morphine daily for four years to a 50-year-old woman with chronic uremia following the removal of a kidney. A prosecution expert testified that this was two to three times the dosage necessary for even the most excruciating pain. Thus, the mere presence of an underlying disease or disorder is not enough, if the prescribing exceeds what is reasonably necessary for treatment of that condition.

The same reporting requirements outlined for emergency pain relief are applicable to relief of pain in nonemergencies. If a Schedule II substance is prescribed to an addict, a report must be filed with the California attorney general's office.

Detoxification Treatment of Narcotic Addicts

Detoxification is the primary medical treatment for narcotic addicts. The type of detoxification legally permitted depends primarily on whether it takes place in an institution, state-approved methadone or propoxyphene napsylate program, or outpatient setting. Section 11217.5 of the California Health and Safety Code permits a licensed physician or surgeon to treat and detoxify an addict for addiction in any office or medical facility which, in his or her professional judgment, is medically proper for the rehabilitation and treatment of the addict. Treatment can include administering "those medications and therapeutic agents which, in the judgment of such physician and surgeon, are medically necessary, provided nothing in this section shall authorize the administration of any narcotic drug." It is important to note that this provision authorizes only the administration of nonnarcotic medications. "Administer" is defined to mean the direct application of a controlled substance, whether by injection, inhalation, ingestion or any other means, to the body of a patient for his immediate needs, either by the practitioner himself, or in the presence of the practitioner by his authorized agent or the patient (*People vs Anderson,* 29 Cal App 3d 551, 1972). An addict or habitual user given nonnarcotic drugs by a private physician does not have to be registered with the attorney general or reported to any law enforcement agency.

The major problem for physicians is to provide an office-based detoxification regimen that is legal and effective. A detoxification regimen for outpatient use that does not contain any drugs in the California Uniform Controlled Substances Act is given in Table 2. This method is described as symptomatic detoxification because medications are prescribed for each symptom (such as pain, myalgia, nausea or insomnia) as opposed to treatment of addiction.[5] It can be used by any California physician in any medical setting. Clonidine, a noncontrolled substance used for treating hypertension, recently has been reported to be effective in narcotic withdrawal, but early observations by one of the authors (F.S.T.) indicate that it is unpredictable in suppressing heroin abstinence symptoms.[6]

When methadone or propoxyphene napsylate (Darvon-N), in higher than symptomatic pain-relieving doses, is used for heroin detoxification or long-term maintenance, special legal approval is required. Section 11217 of the California Health and Safety Code, and Section 4351 of the Welfare and Institutions Code stipulate that the California Department of Health Services' approval

TABLE 2.—*A Symptomatic Narcotic Detoxification Regimen for Use by Physicians**

Drug	*Symptoms*	*Dosage*
Carisoprodol 300 mg (Soma)	Tenseness, anxiety, muscle spasm, insomnia	Give 4 times per day
Pentazocine 50 to 100 mg (Talwin)	Pain	Every 4 to 6 hours
Prochlorperazine 10 mg (Compazine)	Nausea	Give 4 times per day

*The above regimen is for the first day of detoxification, and dosages on subsequent days should be lowered sequentially so that all medications are stopped within 10 to 14 days. These regimens can be be used in any medical setting because they do not involve any California-controlled substance and treat a symptom rather than addiction. Use of this regimen does not require registration of a patient.

TABLE 3.—*Dosages of Schedule II Narcotics Allowed in Narcotic Detoxification Treatment*

*Drugs**	*0-15 Days*	*16-30 Days*
Opium	520 mg	260 mg
Morphine	260 mg	130 mg
Opium alkaloids (Pantopon)	390 mg	195 mg
Hydromorphone (Dilaudid)	65 mg	32 mg
Meperidine (Demerol)	400 mg	200 mg

*These drugs can be used only in state or county hospital, jail, prison, or state-approved facilities, and patients must be registered with the California attorney general. No more than one of the above drugs may be furnished, and all drugs must be discontinued at the end of 30 days from the first treatment.

is necessary for outpatient methadone treatment. Section 11480 of the California Health and Safety Code has established a Research Advisory Panel for controlled substances research. While the approved pain-relieving dose is 400 to 600 mg per day, the dosage required for treatment of addiction without use of ancillary medications is about 1,000 to 1,400 mg per day.[7] Regulations for methadone and propoxyphene napsylate approval have been published.[8-10] Propoxyphene napsylate (Darvon-N) has recently been classified as a federal Schedule IV narcotic. Use of this drug for narcotic treatment requires research approval from the United States Food and Drug Administration (FDA), Drug Enforcement Agency and California Research Advisory Panel.[9,10]

In the treatment of drug addiction involving the use of narcotic drugs other than methadone, the California Health and Safety Code (Section 11217) imposes numerous significant limitations. Treatment can only take place in a state or county hospital, a jail or prison, or a facility approved by the California Department of Health Services. Only a physician or a registered nurse can administer the drugs. Dosages are strictly in acordance with the schedule presented in Table 3.

Medical Maintenance Therapy for Narcotic Addicts

Methadone regulations found in the California Administrative Code and in the *Federal Register* define medical maintenance therapy for a narcotic addict as the administration of medication for longer than 21 days.[8,9] The use of methadone or propoxpyhene napsylate (Darvon-N) for narcotic maintenance treatment requires approvals as described above. Noncontrolled substances for maintenance treatment of psychiatric problems frequently associated with addiction may be prescribed to narcotic addicts and habitual users by any physician in any medical setting. This form of maintenance includes such therapies as tricyclic antidepressant agents for depression, benzodiazepine drugs for anxiety and phenothiazine drugs for thought disorder or psychosis.

Definition and Diagnosis of Narcotic Addicts and Habitual Users

The challenge that confronts physicians is to realize that all controlled substances are not narcotics and to determine whether a patient is an addict or habitual user of narcotic drugs, because the Uniform Controlled Substances Act of the California Health and Safety Code, Section 11156, provides that

> no person shall prescribe for or administer, or dispense a controlled substance to an addict or habitual user, or to any person representing himself as such, except as permitted by this division.

Narcotics are pharmacologically best defined as compounds that provide pain relief, produce tolerance, result in withdrawal signs and symptoms after chronic use, and suppress morphine withdrawal if chronic morphine administration is suddenly discontinued.[11-13] Many barbiturates, amphetamines, stimulants and sedative-hypnotic agents are classified as controlled substances because of their potential for abuse, but do not legally or pharmacologically meet the definition of a narcotic. The legal definition of "narcotic" is given in Section 11019 of the California Health and Safety Code, and includes opium and opiates, any salt, compound derivative or preparation thereof, and any chemical equivalents. It also includes cocaine, which does not correspond to the pharmacological definition.[11-13] Pentazocine (Talwin) and propoxyphene (Darvon) are not yet scheduled under the California Uniform Controlled Substances Act, although they meet pharmacological definitions of narcotics.[14-17] In addition, both bind to the opiate receptor site as do all other narcotics classified under the Uniform Controlled Substances Act.[18] Propoxyphene and pentazocine are now listed on Schedule IV of the Federal Controlled Substances Act.[19] Chronic users of propoxyphene or pentazocine in California may not be legally classified as narcotic addicts or habitual users, although medically they must be considered addicts or habitual users of narcotics.[14-17] Table 1 lists the common commer-

cially available narcotics and their respective schedule in the California Uniform Controlled Substances Act.

The California Health and Safety Code contains no definition of a narcotic addict or habitual user of narcotics. The California Welfare and Institutions Code, Section 3050, however, provides for compulsory civil commitment of addicts, and in that context, the courts have had occasion to carefully define the term "addict." In the case of *People vs Victor* (62 Cal 2d 280, 301-305, 1965), the requisites of addiction were said to be (1) emotional dependence on the drug in the sense that the user experiences a compulsive need to continue its use; (2) a tolerance to its effects which leads the user to require larger and more potent doses, and (3) physical dependence so that the user suffers withdrawal symptoms if he is deprived of his dosage (see also *People vs O'Neil* [62 Cal 2d 748, 752-756, 1965]). In the case of *Elder vs Board of Medical Examiners* (241 Cal App 2d 247, 1966), this definition was used to conclude that a physician who regularly prescribed the controlled substance methamphetamine, to be taken once, twice or three times a day as a treatment for "ex-addicts," was in violation of the law. The court further concluded that the treatment of postwithdrawal symptoms with a controlled substance remains treatment of addiction, and the addict remains an addict while his condition is sustained by a substitute controlled substance. In upholding the revocation of Dr. Elder's license to practice medicine, the court declined to judge the merits of his course of treatment, saying:

> It is not for this court to determine whether or not he was a Dr. Dooley or Dr. Schweitzer for the addicted denizens of the pavement jungle, or whether there are better methods of treating narcotic addicts than those which are provided by law. By his own admissions he had set up a course of treatment for those who admittedly have all the characteristics of addicts as defined in law and medicine.

The term "habitual user" is difficult to define, although some legal precedent has been established. Where the term is used alone, the courts have concluded the term is too vague, indefinite and uncertain, except as applied to addicts (*McCurty vs Board of Medical Examiners,* 180 Cal App 2d 760, 1960). Because the California Health and Safety Code, Section 11156, refers to both addicts and habitual users, however, its apparent broader legal coverage was intended. Thus, compulsive need to continue use alone appears to be sufficient to legally characterize a person as an "habitue" even though tolerance to and physical dependence on the narcotic do not exist.

TABLE 4.—*Minimal Criteria Recommended to Establish Absence of Narcotic Addiction or Habitual Use*

History
Patient denies any narcotic use in past month
Physical examination
Pupil size between 3 and 6 mm
No needle marks on extremities
No withdrawal signs of piloerection, rhinorrhea, lacrimation or diaphoresis
No signs of sedation, decreased reflexes or motor impairment

The general prohibition of Section 11156 of the California Health and Safety Code also extends to any person representing himself as an addict or habitual user, thus including the undercover investigator posing as an addict. In the case of *People vs Nunn* (46 Cal 2d 400, 1956), the court upheld the criminal conviction of a physician who wrote a prescription for 60 tablets of 1/16 grain hydromorphone (Dilaudid) to an undercover state narcotics inspector who told the doctor, "I am using H." The doctor replied, "I cannot write a prescription for heroin, but I can write for some legitimate drug like morphine or Dilaudid." The court found this was sufficient evidence to prove both that the inspector "represented himself to be an addict" and that the doctor knew he was an addict.

Whether it is necessary to prove actual knowledge on the part of the prescribing physician that the patient is an addict or habitual user remains an unsettled question. On the one hand, it seems unreasonable to hold a doctor strictly responsible when he has no reason to believe a patient is addicted. Many addicts make a career out of deceiving doctors and present very convincing complaints to obtain prescriptions for narcotics.[20] On the other hand, requiring actual knowledge would provide a convenient loop-hole for unethical physicians to avoid responsibility simply by not asking the right questions. A court is likely to adopt a middle ground, holding a physician liable if he or she should have known the patient was an addict. The most cursory history and physical examination, however, will usually provide a physican with reason to suspect a patient is addicted. Table 4 lists our minimal recommendations to determine the absence of addiction or habitual use of narcotics. Prescribing any con-

trolled substance without a good faith prior examination is itself a criminal offense, whether the patient is an addict or not, according to the California Business and Professions Code (*People vs Superior Court,* County of Orange, James Dewitt Douglas, Real Party in Interest, 85 Cal App 3d 734, 1978).

Laws in Other Western States

The medical regimens outlined here are equally available to physicians in Alaska, Arizona, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington and Wyoming. Unlike California, these states do not specifically limit prescribing to addicts, nor do they require such prescribing to be specially reported. The only limitation imposed on a physician by these states is that a prescription be issued in the course of "legitimate medical practice." While there are few court decisions in these states which explicate what "legitimate medical practice" is, at least those states which have adopted the Uniform Controlled Substances Act (Hawaii, Idaho, Montana, Nevada and Washington) will probably follow the interpretation given by the federal courts to similar language contained in the Federal Comprehensive Drug Abuse Prevention and Control Act of 1970, on which the Uniform Controlled Substances Act was modelled. In that context, it has been held in the decision of *United States vs Rosen* (582 F, 2d 1032, 1978) that legitimate medical practice can include dispensing a moderate amount of drugs to a known addict in a good faith attempt to treat the addiction or to relieve conditions or suffering incidental to the condition. Cases finding a physician's prescribing to be outside the boundaries of "legitimate medical practice" have generally involved very blatant practices, such as issuing large numbers of prescriptions without physically examining the patient. In one recent case, the United States Supreme Court upheld the criminal conviction of a physician who wrote over 100 prescriptions a day for methadone for 54 days. In concluding that these prescriptions exceeded the bounds of professional practice, the Court noted in the decision of *United States vs Moore* (423 US 122, 1975) that

> he gave inadequate physical examinations or none at all. He ignored the results of the tests he did make. He did not give methadone at the clinic and took no precautions against its misuse and diversion. He did not regulate the dosage at all, prescribing as much and as frequently as the patient demanded. He did not charge for medical services rendered, but graduated his fee according to the number of tablets desired. In practical effect, he acted as a large-scale "pusher"—not as a physician.

For California physicians, prescribing is more regulated. Not only must a prescription meet the minimum threshold of "legitimate medical practice," it must also comply with specific statutory limitations which are unique to California law.

Comment

Various types of errors may occur because a physician does not understand rather complex narcotic laws and regulations. In some instances a physician may unknowingly violate narcotic regulations or withhold appropriate pain relief for fear of addicting a patient. As do all laws and regulations, the narcotic regulations contain some ambiguities, cumbersome restrictions, and perhaps even some irrational aspects. They do, however, allow for safe and effective treatment of pain, detoxification or medical maintenance of an addict, and case law shows examples to illustrate this.

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in memoriam

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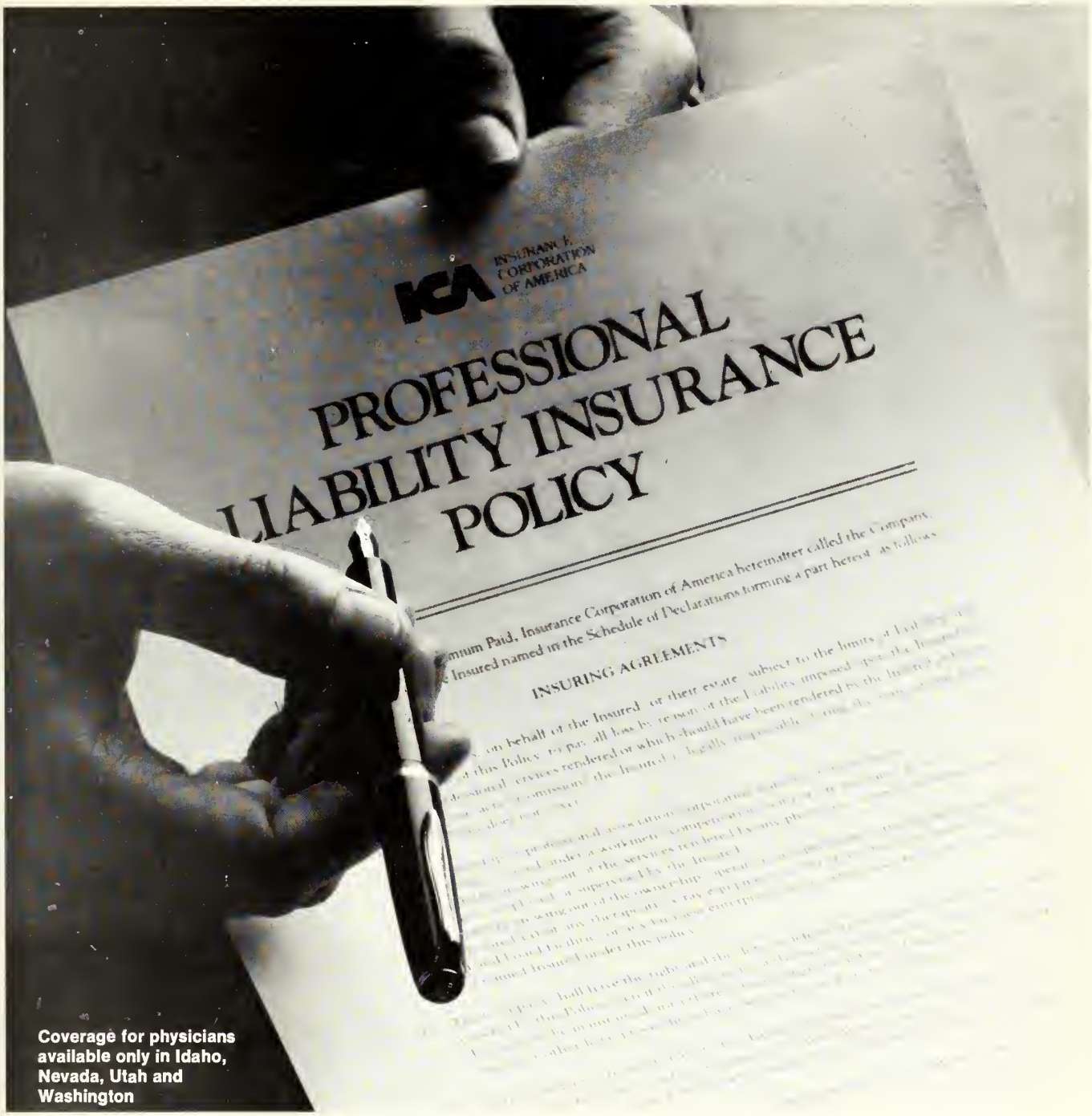

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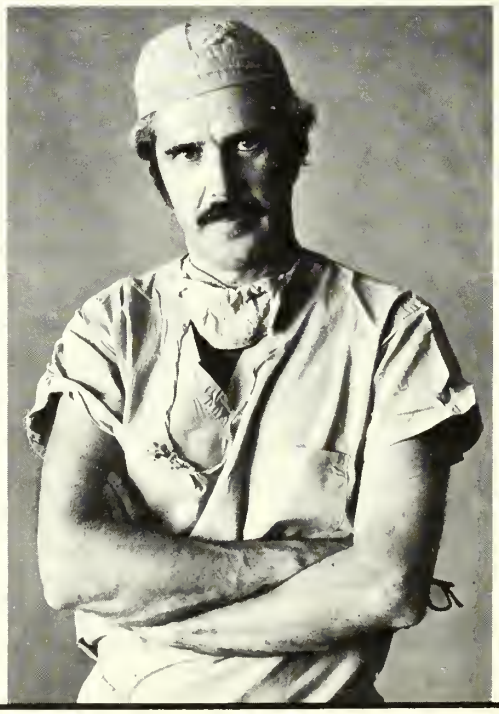

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF GERONTOLOGY & GERIATRICS—VOLUME 1—Editor-in-Chief: Carl Eisdorfer, PhD, MD, University of Washington, Seattle; Associate Editors: Richard W. Besdine, MD, James E. Birren, PhD, Vincent Cristofalo, PhD, M. Powell Lawton, PhD, and George L. Maddox, PhD; Managing Editor, Bernard D. Starr, PhD, C.U.N.Y. Brooklyn College and Graduate Center, C.A.S.E. Springer Publishing Company, 200 Park Ave. South, New York City (10003), 1980. 431 pages, $25.00.

ASSESSMENT OF ENERGY METABOLISM IN HEALTH AND DISEASE—Report of the First Ross Conference on Medical Research. Ross Laboratories, Columbus, OH (43216), 1980. 153 pages.

BASIC & CLINICAL IMMUNOLOGY—Third Edition—Edited by H. Hugh Fudenberg, MD, Professor and Chairman, Department of Basic and Clinical Immunology and Microbiology, Medical University of South Carolina, Charleston; Daniel P. Stites, MD, Associate Professor of Laboratory Medicine and Medicine, Director, Immunology Laboratory; Joseph L. Caldwell, MD, Assistant Professor of Medicine, Fort Miley Veterans Administration Medical Center, and University of California, San Francisco; and J. Vivian Wells, MD, Senior Staff Specialist in Clinical Immunology, Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 782 pages, $17.50.

BASIC PSYCHOTHERAPEUTICS: A Programmed Text—C. Warner Johnson, MD, John R. Snibbe, PhD, and Leonard A. Evans, PhD, University of Southern California School of Medicine, Los Angeles. SP Medical & Scientific Books, 175-20 Wexford Terrace, Jamaica, NY (11432), 1980. 597 pages, $14.95 (paperback).

BIOLOGICAL MONITORING METHODS FOR INDUSTRIAL CHEMICALS—Randall C. Baselt, PhD, Associate Professor, Department of Pathology; Director, Toxicology and Drug Analysis Laboratory, University of California Davis Medical Center, Sacramento. Biomedical Publications, P.O. Box 495, Davis, CA (95616), 1980. 301 pages, $47.00.

BUSSELTON NORMS—Statistics of the Physiological Variables Measured at the Busselton Health Survey, 1972—N. S. Stenhouse, The Raine Medical Statistics Unit, The University of Western Australia, 1979. 110 pages, $8.50; Exclusive Distributor: ISBS, Inc., P.O. Box 555, Forest Grove, OR 97116.

CURRENT OBSTETRIC & GYNECOLOGIC DIAGNOSIS & TREATMENT—Third Edition—Ralph C. Benson, MD, Professor of Obstetrics & Gynecology and Emeritus Chairman, Department of Obstetrics & Gynecology, University of Oregon Health Sciences Center, Portland, and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 1001 pages, $21.00.

DRUG IDENTIFICATION GUIDE—Sixth Edition—adapted from PDR—Medical Economics Books, Box 157, Florence, KY (41042), 1980. 116 pages, $6.95 (soft cover).

FOOT NOTES—Michelle Arnot. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1980. 164 pages, $5.95 (paperback).

THE HUMAN PATIENT—Naomi Remen, MD, Synthesis Graduate School for the Study of Man, and Associate Director, Collaborative Health Program of the San Francisco Consortium. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1980. 238 pages, $10.95.

IMPROVING PATIENT MEDICATION COMPLIANCE—Robert T. Weibert, PharmD, Associate Clinical Professor, University of California, San Francisco, School of Pharmacy, San Diego Program; and Donald A. Dee, RPh, MS, Executive Director, Minnesota State Pharmaceutical Association, St. Paul, and adjunct Assistant Professor, University of Minnesota. Medical Economics Books, Box 157, Florence, KY (41042), 1980. 172 pages, $9.50, plus $1 handling (softbound).

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MESMERISM: A Translation of the Original Scientific and Medical Writings of F. A. Mesmer, MD—Translated and compiled by George Bloch, PhD. William Kaufmann, Inc., One First St., Los Altos, CA (94022), 1980. 152 pages, $11.50 (cloth).

MICROBIAL DISEASES—Notes, Reports, Summaries, Trends—Compiled by Carl W. May, Editor, **The Biology Bookist.** William Kaufmann, Inc., One First Street, Los Altos, CA (94022), 1980. 322 pages, $7.95 (paperback), $14.00 (hardcover).

MOUNTAINEERING MEDICINE—A Wilderness Medical Guide: Ninth Edition—Fred T. Darvill, Jr., MD. Skagit Mountain Rescue Unit, Inc., P.O. Box 2, Mount Vernon, WA (98273), 1980. 55 pages, $1.95.

OPTIONS, SPINAL CORD INJURY AND THE FUTURE—Barry Corbet. National Spinal Cord Injury Foundation, 369 Elliot Street, Newton Upper Falls, MA (02164), 1980. 152 pages, available through National Spinal Cord Injury Foundation.

REVIEW AND ASSESSMENT IN FAMILY PRACTICE—Ernest Yuh-Ting Yen, MD, MPH, DrPH, Associate Professor, Department of Family Medicine, University of North Dakota, Grand Forks. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1980. 184 pages, $12.95.

REVIEW OF MEDICAL PHARMACOLOGY—Seventh Edition—Frederick H. Meyers, MD, Professor of Pharmacology; Ernest Jawetz, MD, PhD, Professor of Microbiology and Medicine; and Alan Goldfien, MD, Professor of Medicine, Departments of Medicine and Obstetrics & Gynecology and Cardiovascular Research Institute; University of California, San Francisco, School of Medicine. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 747 pages, $17.50.

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY AND OTHER SELECTED COMPUTER TOPICS—Proceedings of the 10th Annual Symposium, Society of Nuclear Medicine Computer Council, January, 1980, Miami Beach—Book Coordinator: James A. Sorenson, PhD, University of Utah Medical Center, Salt Lake City. The Society of Nuclear Medicine, 475 Park Avenue South, New York City (10016), 1980. 244 pages, no price given.

SOUND SLEEP—Quentin R. Regerstein, MD, Assistant Professor of Psychiatry, Harvard Medical School, and Director, Sleep Clinic, Peter Bent Brigham Hospital, Boston; with James R. Rechs, professional writer. Simon and Schuster, Simon & Schuster Building, Rockefeller Center, 1230 Avenue of the Americas, New York City (10020), 1980. 208 pages, $10.95.

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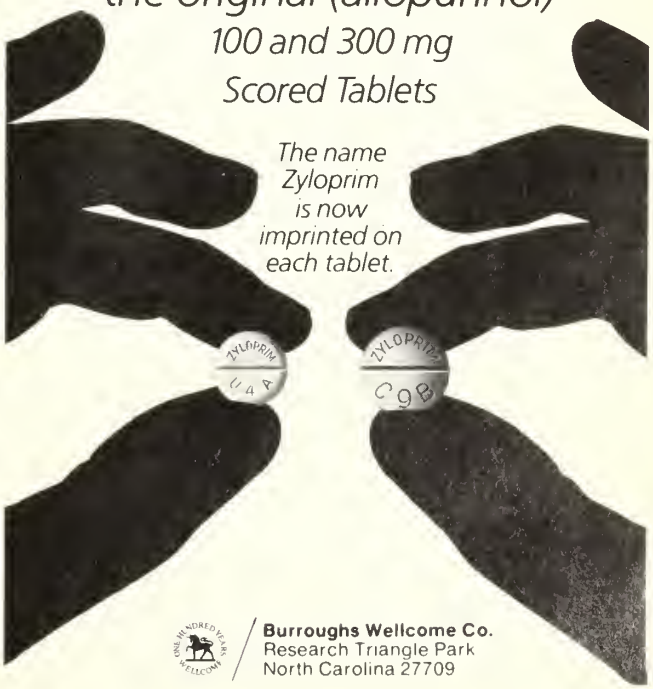

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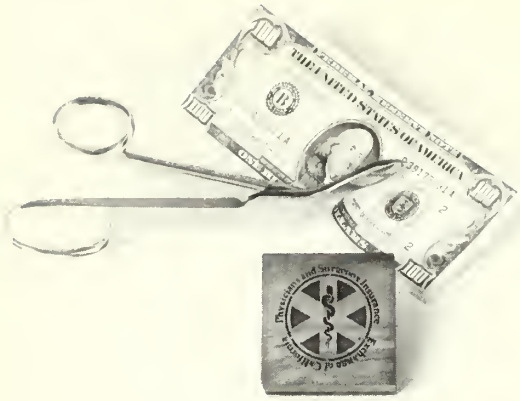

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ANESTHESIOLOGY

January 6-10—**Anesthesia Update.** UCSD at Hotel del Coronado, Coronado. Tuesday-Saturday. 20 hrs. $250.

January 23-25—**Pediatric Anesthesiology—19th Clinical Conference.** Childrens Hospital of Los Angeles at Marriott Hotel, Los Angeles. 15 hrs. $165. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 14-21—**9th Obstetric Anesthesia Conference.** Ohio State Univ. at Sheraton Waikiki, Honolulu. One week. 25 hrs. Contact: Excursions Unlimited, Inc., c/o OSU Dept. of Anesthesiology, 1820 Northwest Blvd., Columbus, OH 43212. (800) 848-4438.

CANCER

January 22-24—**Current Concepts in Cancer Diagnosis.** UCLA at Century Plaza Hotel, Los Angeles. Thursday-Saturday.

January 23-24—**Cancer Update 1981.** Peralta Hospital at Goodman's Hall, Jack London Square, Oakland. Friday-Saturday. 10 hrs. Contact: Susan Ford, Education and Training Dept., Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 2327.

January 24-25—**Current Approaches to Radiation Oncology.** UCSF at Sir Francis Drake Hotel, San Francisco. Saturday-Sunday.

January 30-February 1—**Midwinter Oncology Conference—for Radiation Oncologists.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $150. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

February 5-9—**Controversies in Lung Cancer.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Monday. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** See Medicine, February 23-26.

February 25—**Ovarian Cancer.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

February 28-March 1—**Recent Advances in Cancer Diagnosis.** UCLA. Saturday-Sunday.

March 6-8—**Current Approaches to Radiation Oncology, Biology and Physics.** See Radiology, March 6-8.

March 8-13—**19th National Conference on Breast Cancer.** American College of Radiology, American Cancer Society, College of American Pathologists at Hotel del Coronado, Coronado. Sunday-Friday. 33 hrs. $275. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, MD 20015. (301) 654-6900.

March 13-14—**Childhood Cancer: Triumph Over Tragedy—16th Annual Cancer Symposium.** West Coast Cancer Foundation and Calif. Division of American Cancer Society at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. $110 before February 1; $130 thereafter. Contact: WCCF, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

April 25—**Oncology Update: 1981.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. 8 hrs. $125. Contact: Sandra Rozzen, Dept. of Med. Ed., Northridge Hosp., 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

May 18-22—**Medical Oncology Review.** American College of Physicians at University of Hawaii School of Medicine, Honolulu. Monday-Friday. Contact: Postgraduate Dept., ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

EMERGENCY MEDICINE

January 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

January 21-23—**Sierra Traumatological Society.** See Surgery, January 21-23.

January 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

February 16-19—**Emergency Medicine: New Concepts in Re-**

KEY TO ABBREVIATIONS

CMA: California Medical Association
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DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

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UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
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Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

cal Education Corp at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 1-2—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton Fisherman's Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 2-3—**Practical Dermatology.** UCLA at Santa Barbara. Saturday-Sunday.

May 6—**Respiratory.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

May 7-9—**Cardiovascular Emergencies.** American College of Cardiology and PMC at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. 18 hrs. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

May 8-10—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

May 23-30—**Allergy and Immunology.** Univ. of Washington School of Medicine at Wailea Beach, Maui, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195.

May 31-June 4—**Internal Medicine for the Generalist—1981.** UCSD at Hilton, San Diego. Sunday-Thursday. 23 hrs.

OBSTETRICS AND GYNECOLOGY

January 10-16—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

January 14-17—**Postgraduate Course on Basic and Advanced Gyn Urology: Theory and Practice.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Wednesday-Saturday. 20 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 25-30—**Obstetrics-Gynecology Update: 1981.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

January 26-30—**10th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday. 36 hrs. $400.

February 7-8—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. Contact: Dee Davis, Exec. Sec., LAOGS, 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

April 4-11—**Current Concepts in Ob/Gyn.** Univ. of Washington School of Medicine at Kona Surf Hotel, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 10-11—**26th Annual T. Hart Baker, MD, Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at South Coast Plaza Hotel, Costa Mesa. Friday-Saturday. Contact: Lilia M. Guerrero, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

May 11-13—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 18 hrs.

PEDIATRICS

January 14—**20th Annual Parmelee Memorial Lecture and Neonatal Symposium.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday. $75, members; $100, nonmembers. Contact: LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

January 25-28—**6th Annual Pediatric Winter Ski and Study Symposium.** American Academy of Pediatrics, Calif. Chap. 2, at Mammoth Mountain. Sunday-Wednesday. $160, members; $185, nonmembers. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

February 4-6—**Children With Heart Disease.** See Medicine, February 4-6.

February 17-20—**Epilepsy in Childhood and Adolescence—32nd Annual Western Institute on Epilepsy.** See Medicine, February 17-20.

March 12-15—**Clinical Pediatrics.** American Academy of Pediatrics, Calif. Chap. 2, at Hilton Riviera, Palm Springs. Thursday-Sunday. $160, members; $185, nonmembers. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 3-4—**Pediatric Topics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 8-10—**Update in Pediatric Pulmonary and Intensive Care.** See Medicine, April 8-10.

May 2-3—**The Physician and the Handicapped Child: New Directions.** American Academy of Pediatrics and State Dept. of Education at Sacramento. Saturday-Sunday. Contact: Peter Miller, MD, Marin Co. Civic Ctr., Rm. 280, Dept. of Health and Human Services, San Rafael 94903. (415) 499-6877.

May 4-8—**11th Annual Review of Pediatrics.** USC. Monday-Friday.

May 6-8—**Care of the Sick Newborn—6th Annual Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 13—**Genetic Counseling.** LLU. Wednesday. 4 hrs. $30.

May 14-16—**Advances in Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

May 20-25—**Pediatrics for the Primary Care Physician and All That Jazz.** UCD at Sacramento. Wednesday-Monday.

PSYCHIATRY

January 14-May 27—**Practicum on Family Therapy and Schizophrenia.** Mental Research Institute, Palo Alto. Wednesdays. 80 hrs. $600. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 25-31—**7th Annual Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. One week. 26 hrs.

January 30-31—**Heinz von Foerster on Cybernetics, Language, and Understanding.** Mental Research Institute, Palo Alto. Friday-Saturday. 12 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

March 2-4—**Basic Neuroscience and Biobehavioral Science.** STAN. Monday-Wednesday. 15 hrs. $225.

March 4-8—**7th International Gender Dysphoria Symposium.** Univ. of Nevada School of Medicine and Harry Benjamin International Gender Dysphoria Assn. at Cal-Neva Lodge, Lake Tahoe. Wednesday-Sunday. $150. Contact: Marjorie Cutler, Cont. Med. Ed., College Inn, Univ. of Nevada, Reno 89557. (702) 784-4046.

April 3-5—**Cults, Religiosity and the Adolescent.** UCSF. Friday-Sunday.

RADIOLOGY AND PATHOLOGY

January 19-23—**Interventional Radiologic Techniques: Computed Tomography and Ultrasonography.** UCSF at Fairmont, San Francisco. Monday-Friday. $350.

January 19-24—**Review Course in Clinical Ob, Gyn, and Histological Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Monday-Saturday. 41 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 21-23—**8th Annual Postgraduate Course in Genitourinary Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 22½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 24-31—**International Diagnostic Radiology Conference.** UCSF at Maui Surf Hotel, Maui, Hawaii. One week.

January 26-30—**Tumorous Conditions of the Bones and Soft Tissues.** American Society of Clinical Pathologists at San Diego. Monday-Friday. 37½ hrs. $500, ASCP members; $600, nonmembers. Contact: Admin. Asst., Education Ctr., ASCP, 2100 W. Harrison St., Chicago 60643. (312) 738-1336.

January 30-February 1—**33rd Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $150. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

February 4-6—**Recent Progress in Diagnostic Laboratory Immunology.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 24 hrs. $250. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 9-12—**Molecular Basis of Cell-Cell Interaction.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Monday-Thursday. 24 hrs. $165. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 9-13—**New Horizons in Laboratory Medicine.** Univ. of Nevada School of Medicine and American Soc. of Clinical Pathologists at Sahara, Lake Tahoe. Monday-Friday. Contact: Marjorie Cutler, Cont. Med. Ed., College Inn, Univ. of Nevada, Reno 89557. (702) 784-4046.

February 11—**Neuroradiology—Its Use, Indications and Values in Strokes, Tumors and Head Trauma.** LLU. Wednesday. 4 hrs. $30.

February 18-20—**Anaerobic Bacteriology Methods.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 15 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 25-27—**Minicomputers, Microcomputers and Big Computers.** American Society of Clinical Pathologists at Monterey. Wednesday-Friday. 19½ hrs. Contact: Admin. Asst., Education Center, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

February 27-March 1—**Neuroradiology.** USC. Friday-Sunday. 20 hrs. $200.

February 28—**Cytology Workshop.** UCLA. Saturday.

March 4-7—**Sierra Radiology Conference—2nd Annual.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at North Lake Tahoe. Wednesday-Saturday. 18 hrs. $245. Contact: Michael H. Reid, PhD, MD, Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

March 6-8—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Friday-Sunday.

March 8-13—**19th National Conference on Breast Cancer.** See Cancer, March 8-13.

March 9-13—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $350.

March 13-19—**College of American Pathologists/American Society of Clinical Pathologists—Joint Spring Meeting.** Town and Country, San Diego. Friday-Thursday. Contact: Joan Lipe, CAP, 7400 N. Skokie Blvd., Skokie, IL 60077. (312) 677-3500.

March 14-15—**B-Scan Ultrasonography: Update.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

April 11-18—**Hawaii Imaging Conference.** American College of Medical Imaging at Kauai Surf Hotel, Kauai, Hawaii. One week. 23½ hrs. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

April 25—**Cytology Workshop.** UCLA. Saturday.

May 2-9—**Pathology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

May 24-29—**The Pathologist as a Clinical Consultant.** UCD at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 23 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

January 9-11—**Debates, Controversies and Concepts in the Treatment of the High Risk Patient.** See Medicine, January 9-11.

January 10—**Photocoagulation Therapy.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

January 21-23—**Sierra Traumatological Society—10th Annual Meeting.** Bear Valley. Wednesday-Friday. 6 hrs. Contact: Sierra Traumatological Soc., P.O. Box 230, Stockton 95201. (209) 466-9535.

January 23-24—**Third Annual Postgraduate Course in Surgery.** UCD at Point West Hotel, Sacramento. Friday-Saturday. 14 hrs. $85.

January 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

January 25-28—**Society of Thoracic Surgeons—17th Annual Meeting.** Bonaventure Hotel, Los Angeles. Sunday-Wednesday. Contact: W. G. Purcell, Bus. Mgr., STS, 111 E. Wacker Dr., Chicago 60601.

January 25-30—**Assembly in Surgery—4th Annual.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sunday-Friday. 28 hrs.

February 4-6—**Current Thinking in the Management of Ocular and Adnexal Tumors.** UCSF. Wednesday-Friday.

February 5-7—**Aesthetic Rhinoplasty and Nasal Reconstruction.** UCLA. Thursday-Saturday.

February 6-8—**National Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery and American Society for Dermatologic Surgery at Ramada Inn, Beverly Hills. Friday-Sunday. Contact: Drs. Richard Fleming, Toby Mayer, Peter Goldman, 9730 Wilshire Blvd., Ste. 216, Beverly Hills 90212.

February 8-10—**The Mandible: Surgical Treatment of Congenital and Acquired Deformities.** UCLA. Sunday-Tuesday.

February 14-20—**Neurological Surgery of the Ear and Skull Base—3rd International Workshop.** Ear Research Institute at Newporter Inn, Newport Beach. One week. 32 hrs. $500. Contact: Derald E. Brackmann, MD, Neurological Workshop, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

Februry 20-22—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** See Medicine, February 20-22.

February 23-25—**American Society for Surgery of the Hand—36th Annual Meeting.** Las Vegas. Monday-Wednesday. Contact: ASSH, 2600 S. Parker Rd., Suite 132, Aurora, CO 80014. (303) 755-4588.

February 26-March 3—**American Academy of Orthopaedic Surgeons.** Convention Center, Las Vegas. Thursday-Tuesday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

March 5-7—**Calculi.** American Urological Association at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: AUA, Office of Education, Texas Med. Ctr., 4th Fl-Inst. of Religion Bldg., 1129 Wilkins, Houston, TX 77030.

March 6-7—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 11—**Common Fractures and Joint Injuries.** LLU. Wednesday. 4 hrs. $30.

March 21-22—**ECG Course for Oral and Maxillofacial Surgeons.** UCSF. Saturday-Sunday.

March 25-28—**4th Annual U.S. IOL Symposium.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Wednesday-Saturday. Contact: Debbi Miller, Dir. of Mtg. Services, Am. Intra-Ocular Implant Soc., P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

March 26-29—**Pediatric Surgery of the Head and Neck: A Frontier Symposium.** The Institute for Medical Education and Research and UCSD at Silverado Country Club and Resort, Napa Valley. Thursday-Sunday. 20 hrs. Contact: The Institute for Medical Education and Research, 135 Dickinson St., San Diego 92103.

April 4-8—**Seminar on Controversial Surgery—18th Annual.** UCLA at Hilton Riviera, Palm Springs. Saturday-Wednesday. 18 hrs. $295.

April 8—**Urology.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

April 8-11—**Facial Plastic Surgery Symposium.** UCSF. Wednesday-Saturday.

April 8-12—**Symposium on Vascular Surgery—9th Annual.** UCLA at Hilton Riviera, Palm Springs. Wednesday-Sunday. 18 hrs. $315.

April 9-10—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 9-11—**General Surgery.** UCSF. Thursday-Saturday.

April 23-24—**XII Jules Stein Lecture and Annual Postgraduate Seminar—Anterior Segment Disease: Current Update on Immunology, Corneal Disease, Refractive Surgery, and Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

April 25—**Radial Keratotomy Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

May 9-16—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $295.

May 21-22—**Neurosurgery—11th Annual Postgraduate Course.** UCSF. Thursday-Friday.

OF INTEREST TO ALL PHYSICIANS

January 9-10—**New Concepts in Management of Chronic Pain.** Bay General Community Hospital at Half Moon Inn, Shelter Island, San Diego. Friday-Saturday. 10 hrs. $45. Contact: Karen Johnson, Bay Gen. Community Hosp., 435 H St., Chula Vista 92010. (714) 420-8182.

January 14—**Sexual Therapy.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Memorial Hosp, 5th Ave and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

January 17—**The Myths and Realities of Genital Herpes: What Patients Need to Know.** UCLA. Saturday. 5 hrs. $25.

January 22-24—**Modern Drug Therapy.** STAN. Thursday-Saturday. 15 hrs. $225.

January 23—**Diagnosis and Treatment of Sleep Disorders Patients.** STAN at Marriott, Santa Clara. Friday. 7 hrs. $35.

January 26-31—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. One week. 50 hrs. Contact: Cont. Ed. in Health Sciences, UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

February 6-12—**Annual Mid-Winter Seminar.** Grossmont Hospital at South Lake Tahoe. One week. 13 hrs. $50. Contact: Grossmont Hospital, CME Committee, P.O. Box 158, La Mesa 92041.

February 11-13—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Wednesday-Friday. 22 hrs. $275.

February 19-22—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Thursday-Sunday. 14 hrs.

February 20-21—**Pain: New Approaches to Treatment.** Mesa Vista Hospital and Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Virginia Everett, Vista Hill Fndn., 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 23-27—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $295.

February 26-27—**Therapeutic Drug Monitoring.** PMC. Thursday-Friday. 12 hrs. $85.

March 1-5—**Medical Evaluation of the Preoperative Patient.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Thursday.

March 3-June 30—**Family Medicine.** USC. Tuesdays; 7:00-10:15 p.m. 56 hrs. $325.

March 5-8—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Thursday-Sunday.

March 5-8—**Sports Medicine.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday.

March 13-15—**Clinical Management.** STAN at The Lodge, Pebble Beach. Friday-Sunday. 8 hrs.

March 13-18—**California Medical Association—110th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 16-20—**Sports Medicine.** University of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $230. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 16-27—**Intensive Residency in Occupational Medicine, Session II.** UCSF. Two weeks.

March 18-20—**Recent Advances in Clinical Nutrition.** UCSD at Vacation Village, San Diego. Wednesday-Friday. 17 hrs.

March 21—**Alcoholism and Its Treatment: 1981.** UCD at Hotel El Rancho Racquet Resort, Sacramento. Saturday. 7½ hrs.

April 8—**Psychiatry for the Non-Psychiatrist.** LLU. Wednesday. 4 hrs. $30.

April 11-12—**Nutrition for the Primary Care Physician.** UCSF. Saturday-Sunday. 14 hrs. $125.

April 11-18—**Office Management of Chronic Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 11-18—**Drug Therapy.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 12-14—**Family Problems, Aging and Sexuality.** USC. Sunday-Tuesday. 18 hrs. $136.

April 23-25—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 23-26—**Wound Management Workshop.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

April 25-26—**Pharmacokinetics '81.** Memorial Hospital Medical Center—UCI Center for Health Education, Long Beach. Saturday-Sunday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 25-May 2—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $350.

May 5-11—**Basic Diving Medicine.** UCSF. One week.

May 11-15—**Postgraduate Institute for Primary Care Physicians—Symposium on Non-Emergency Outpatient Care.** UCSD at Vacation Village, San Diego. Monday-Friday. 27 hrs. $275.

May 16-17—**Eating Disorders.** UCLA. Saturday-Sunday.

May 17-22—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Thursday.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Margaret H. Griffith, Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded sum-

maries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed –12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

January 28—**Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

February 5—**Endorphins—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 19—**Right Brain Functioning—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 25—**Gardnerella Vaginalis Vaginitis—Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

April 30—**Group Therapy—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

May 27—**Univ. of Wash. Ob/Gyn Session** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

June 18—**Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

January 21-25—**Sexually Transmitted Diseases—Univ. of Wash. Internal Medicine Review Sessions.**

UNIVERSITY OF CALIFORNIA, SAN DIEGO SCHOOL OF MEDICINE

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University of Colorado School of Medicine
Denver, Colorado

JOHN ALEXANDER-WILLIAMS, MB, ChB, FRCS, *Consultant in Surgery*
The General Hospital
Birmingham, England

For further information, write to: **Office of Continuing Education, M-017**
University of California, San Diego School of Medicine
La Jolla, CA 92093

28 Hours
Category I Credit

January 21, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

January 22, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

January 23, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 11—**Pediatric Anesthesiology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 18-20—**Adolescent Medicine—Univ. of Wash. Internal Medicine Review Sessions.**

February 18, Wednesday, Great Falls. 5-7:30 p.m. Deaconess Hospital. Contact F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 19, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

February 20, Friday, Missoula. 8-10:30 a.m. St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 6-7—**Topics in Internal Medicine.** Big Sky. Friday-Saturday. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. 406) 657-7083.

March 25-27—**New Developments in Cardiology—Univ. of Wash. Internal Medicine Review Sessions.**

March 25, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 26, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 27, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 22-24—**Congenital Heart Disease in Adults—Univ. of Wash. Internal Medicine Review Sessions.**

April 22, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 23, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

April 24, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 27-29—**Office Endocrinology—Univ. of Wash. Internal Medicine Review Sessions.**

May 27, Wednesday, Great Falls. 5-7:30 p.m. Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

May 29, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 10—**Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

IDAHO

January 20—**Endocrinology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

February 14-21—**Perinatal Critical Care.** Sun Valley. Saturday-Sunday. Elkhorn Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21-28—**Sports Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 16—**Gyn Oncology—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

March 17—**Infectious Diseases—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 18—**Evaluation and Treatment of Premature Labor—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 19—**Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue. Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 9-13—**Twelfth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

SURGERY

March 6-7—**Surgery.** Portland. Friday-Saturday. Downtown Red Lion. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland 97201. (503) 225-8700.

INTEREST TO ALL PHYSICIANS

April 2-3—**Current Concepts in Drug Therapy.** Portland. Thursday-Friday. Jantzen Beach Thunderbird. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

December 16—**Evaluation of Male Fertility—U/W OB-GYN Sessions** (Spokane). Tuesday. 12:00-1:00 p.m. Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, W. 101 8th Avenue, Spokane, WA 99204. (509) 838-8347.

1981

January 12—**Abdominal Pain.** Seattle. Monday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education and Training Dept., 1551 North 120th, Seattle, WA 98133. (206) 346-0500, Ext. 1737.

January 16-17—**Beta Blocking Agents/Calcium Antagonists.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

January 23—**The Foot.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

January 23-24—**Developmental Disorders in Children.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

January 24—**New Approaches to Gastrointestinal Bleeding.** Tacoma. Saturday. St. Joseph Hospital. Contact: CME Pierce County.

January 25-February 1—**Sports Medicine Seminar.** Maui, Hawaii. Sunday-Sunday. Wailea, Maui, Hawaii. Contact: Sports Visions, Central Way Plaza No. 15, Central Way No. 258, Kirkland, WA 98033.

January 26—**Lipids and Diabetes—U/W Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

January 27—**Univ. of Wash. OB/GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

January 29-30—**Financial Planning for Physicians.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

January 31—**The Care of Normal Children.** Seattle. Saturday. Group Health Hospital, 6th Floor Conference Area. Contact: Jackie Kersh, Office of Medical Education, 201 16th Avenue East, A-5, #321, Seattle, WA 98112. (206) 326-7349.

February 2-6—**Ski & Learn 81.** Crystal Mountain. Monday-Friday. Silver Skis Chalet, Crystal Mountain. Contact: Carolyn M. Palmer, 3700 140th Avenue NE, Bellevue, WA 98005. (206) 883-8852.

February 5-6—**Schizophrenia and Depression.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

February 6-7—**Workshops in Fluid and Electrolyte Disorders.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

February 10—**Anesthesiology and Pediatrics—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

February 12-14—**National Health Service Corps.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

February 14-21—**Perinatal Critical Care.** Sun Valley, ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Sports Medicine.** Sun Valley, ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Practical Neurology.** Ilikai, Honolulu, Hawaii. Saturday-Saturday. U/W at Ilikai, Honolulu, Hawaii. Contact: U/W School of Medicine.

February 21-28—**Metabolism and Endocrinology.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

February 23—**Emergency Medical Services—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD. P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

February 27—**Diagnosis and Treatment of Common Arthritic Diseases.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 5-6—**Preventing/Surviving Stress as a Physician.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

March 6-7—**Clinical Pharmacology for the Practitioner.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 7—**Handicapped Child.** Seattle. Saturday. Contact: U/W School of Medicine.

March 12-13—**Tacoma Academy of Internal Medicine.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 12-13—**Diabetes in General Medicine.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

March 16—**Gyn Oncology—Univ. of Wash. OB/GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 17—**Epilepsy.** Spokane. Tuesday. Contact: U/W School of Medicine.

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

March 23—**Pain—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 23-27—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

March 26-27—**Sexually Transmitted Diseases.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

March 30-April 10—**Rehabilitation Medicine Review.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

April 3—**Nutrition in the Hospitalized Patient.** Seattle. Friday. Contact: U/W School of Medicine.

April 4—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

April 4-11—**Current Concepts in OB/GYN.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Office Management of Chronic Pain.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Wailea, Maui, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Drug Therapy.** Maui, Hawaii. Saturday-Saturday. U/W at Royal Lahaina, Maui, Hawaii. Contact: U/W School of Medicine.

April 14—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

April 16-18—**Modern Diagnostic Techniques: Use/Abuse.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

April 17-18—**Modern Office Procedures: Minor Surgeries.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

April 18-25—**Emergency Medical Care.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

April 27—**Total Parenteral Nutrition—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 30-May 2—**Trauma.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

May 1—**Management of Acute Medical Problems.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 7-8—**Medical Genetics and Teratology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 15-16—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 15-16—**Medical Alumni.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

May 18—**Arrhythmias—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 19—**Evaluation and Treatment of Premature Labor—Univ. of Wash. OB/GYN Sessions.** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 21-22—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 23-30—**Allergy and Immunology.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

June 4-6—**Radiology Northwest V.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 4-5—**Pacific Northwest Chapter of the American College of Chest Physicians: Cardiopulmonary Symposium.** Seattle. Thursday-Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

June 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

June 11-12—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 15-19—**Death Investigation.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

June 18-19—**Respiratory Care.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 22—**Ophthalmology for the Internist—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

July 25-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Saturday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221
SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

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1981

January 7

SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Gastroenterology/Hepatology**
LOCATION: UUMC, Classroom D, 7-9 pm
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

January 17-21

SPONSOR: Utah Ophthalmological Society/University of Utah/Johnson & Johnson
TITLE: **Interocular Lens Course**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 24 hours
CONTACT: A. Thomas Williams, MD (801) 262-6111

January 24-31
SPONSOR: University of Utah
TITLE: **6th Annual Snowbird Radiology Conference**
LOCATION: Snowbird
FEE: To be announced
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8188

January 31-February 7
SPONSOR: University of California, San Francisco, CA
TITLE: **Infectious Diseases in Clinical Practice**
LOCATION: Park City
FEE: $200.00 ($250.00 after October 15, 1980)
CREDIT: 20 hours
CONTACT: Extended Programs in Medical Education
University of California
1308 3rd Avenue
San Francisco, CA 94143
(415) 666-2483 or 666-2894

February 4
SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Arthritis and Rheumatology**
LOCATION: UUMC, Classroom D, 7-9 pm
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

February 9-12
SPONSOR: University of Utah
TITLE: **10th Annual Family Practice Refresher Course**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 28 hours
CONTACT: David N. Sundwall, MD (801) 581-8633

February 15-20
SPONSOR: University of Utah
TITLE: **Update on Clinical Microbiology and Immunology**
LOCATION: Park City
FEE: To be announced
CREDIT: 24 hours
CONTACT: John M. Matsen, MD (801) 581-5514

February 17-20
SPONSOR: Primary Children's Medical Center
TITLE: **Postgraduate Course in Pediatric Surgery**
LOCATION: Park City
FEE: $250.00
CREDIT: 12 hours
CONTACT: Stan Everett (801) 350-1100

February 20-24
SPONSOR: University of Utah
TITLE: **26th Annual Postgrad Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: 16 hours
CONTACT: Theodore H. Stanley, MD (801) 581-6393

February 21-24
SPONSOR: University of Utah
TITLE: **22nd Annual OB-BYN Course**
LOCATION: Holiday Inn, Park City
FEE: $250.00
CREDIT: 15 hours
CONTACT: David H. Engelberg, MD (801) 581-7647

February 22-27
SPONSOR: Utah Ophthalmological Society
TITLE: **OUS Winter Meeting**
LOCATION: Park City
FEE: To be announced
CREDIT: 12 hours
CONTACT: A. Thomas Williams, MD (801) 268-6111

February 25-27
SPONSOR: University of Utah/Intermountain Pediatric Society/
American Academy of Pediatrics
TITLE: **Common Problems in Pediatrics III**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 16 hours
CONTACT: Bruce Buehler, MD (801) 581-7877

February 25-28
SPONSOR: University of Utah
TITLE: **Gynecologic Oncology Course**
LOCATION: To be announced
FEE: To be announced
CREDIT: 15 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-March 7
SPONSOR: University of Utah
TITLE: **Midwinter Radiology Pacific Cruise Meeting**
LOCATION: Departs from Los Angeles
FEE: $300.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

March 6
SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Infectious Disease**
LOCATION: UUMC
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

February 28-March 7
SPONSOR: University of Utah
TITLE: **6th Annual Advances in Internal Medicine**
LOCATION: Snowbird
FEE: $225.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

February 28-March 7
SPONSOR: University of Utah
TITLE: **Nutrition and Contemporary Medicine**
LOCATION: Park City
FEE: $200.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: May 23-27, 1981, Glacier Bay Lodge, Glacier Bay.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 22-26, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1981, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Interim Meeting: April 10-11, 1981, Colonial Inn, Helena. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 6-8, 1981, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Ramada Snow King Inn, Jackson.

March 7-14

SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 14-21

SPONSOR: University of Utah
TITLE: **3rd Annual Park City Radiology Conference: Neuroradiology**
LOCATION: Park City
FEE: $240.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

April 1

SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Clinical Pharmacology**
LOCATION: UUMC
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

April 8-10

SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ University of Arizona Center for Occupational Safety and Health/University of Texas Health Science Center, School of Public Health
TITLE: **3rd Annual Park City Environmental Health Conference: Legal and Ethical Dilemmas in Occupational Health**
LOCATION: Prospector Square Lodge, Park City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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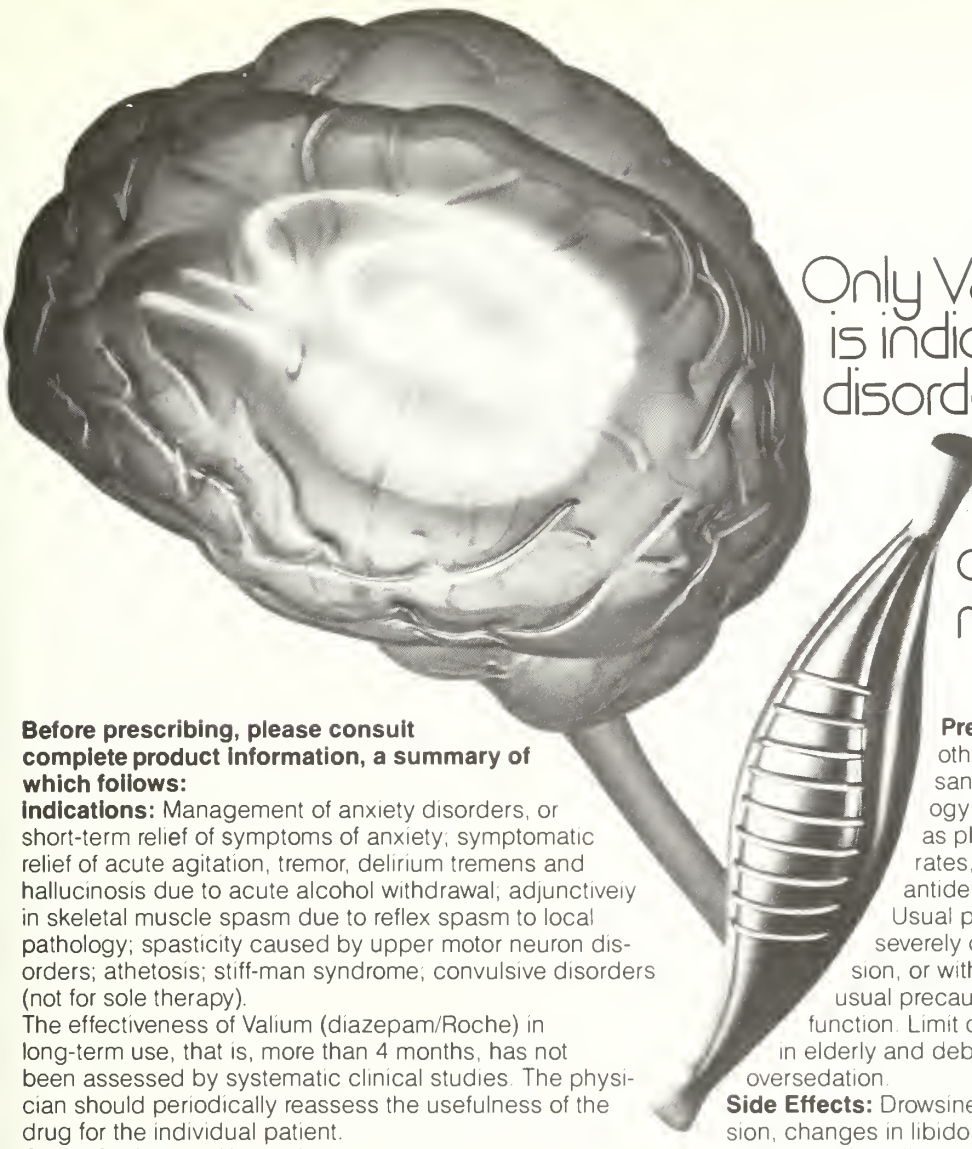

Only Valium® (diazepam/Roche) is indicated in anxiety disorders and as an adjunct in the relief of skeletal muscle spasm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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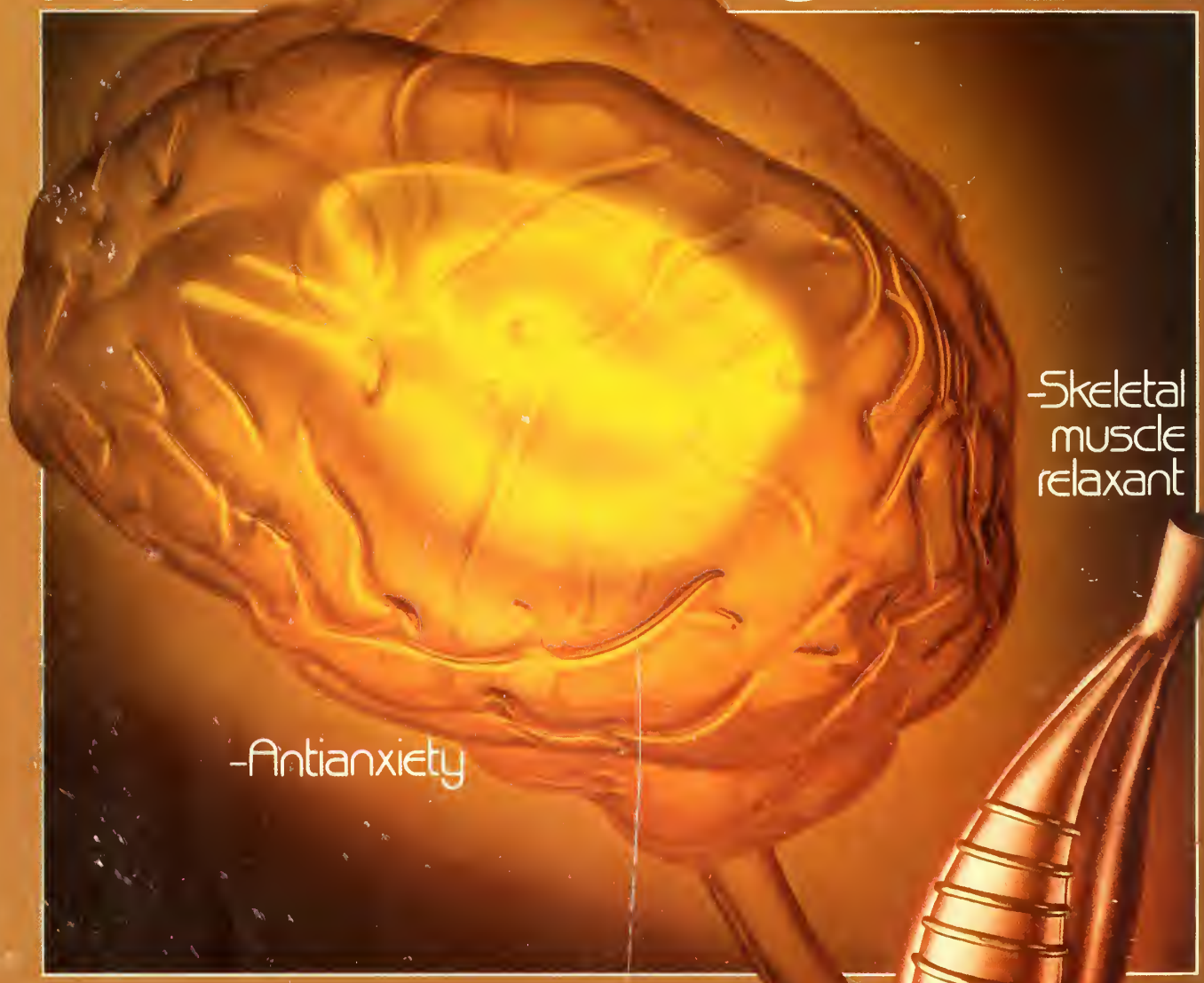

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